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Cognitive progression and care patterns in all-cause dementia by prior cancer diagnosis

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COGNITIVE PROGRESSION AND CARE PATTERNS IN ALL-CAUSE DEMENTIA BY PRIOR CANCER DIAGNOSIS

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EPIDEMIOLOGY

ABSTRACT

Cancer and dementia are common aging-related diseases. Cancer and its treatments are associated with cognitive impairment referred to as cancer-related cognitive impairment (CRCI). Dementias demonstrate similar impairment. Only one study has examined the longitudinal association between cancer and dementia. This dissertation goes beyond limitations of the prior study and has three aims: 1.) to evaluate dementia progression by prior cancer diagnosis, 2.) to evaluate progression of all-cause dementia by cancer treatments, and 3.) to evaluate patterns and predictors of care among dementia patients by cancer history.

This study uses EHR data to evaluate cognitive progression by cancer history / cancer treatment characteristics, and proportion of specialty care visits and predictors of such visits compared to visits in other locations by cancer history among dementia patients.

Results indicate participants with any cancer history have higher baseline cognition than those without cancer history (β: 1.49, 95% CI: 0.91-2.07), and progress slower (β: 0.40, 95% CI: 0.08-0.71). However, adjusting for health behaviors and comorbidities attenuated this association. Although non-Hispanic blacks had lower cognition at baseline compared to the other race and ethnic groups, the only race/ethnic

differences we observed was that people of Other race/ethnic groups had a different cognitive progression than non-Hispanic whites and non-Hispanic blacks. Immunotherapies result in lower mean baseline cognition (15.20 vs. Chemotherapy: 18.40; Hormone therapy: 19.29; Two or more: 20.06) and slower mean progression per year than those on other therapies and two or more therapies (3.35 vs. Chemotherapy: 0.23; Hormone therapy: 0.18; Two or more: -1.52). Finally, those with cancer history are less likely to utilize specialty care than those without on (11.3% vs. 17.1%) or after dementia diagnosis (13.5% vs. 19.2%). Age at dementia diagnosis, Black race, anti-cholinergic burden, socioeconomic status, and vascular risk predict lower odds of specialty care.

This work supports hypotheses of many underlying mechanisms for cancer's effect on dementia. Studies are needed to explore causes of racial disparities and to assess cancer treatments in a larger sample with ability to control for cancer staging and evaluate disparities in this association. Finally, studies are needed to evaluate causes of differences in specialty care utilization between those with and without cancer history.

Keywords: Cancer-Related Cognitive Impairment; Dementia Progression; Aging-Related Disease Burden; Long-Term Effects of Cancer Treatment; Late Effects of Cancer Treatment; Dementia Care Patterns

DEDICATION

Where do I even begin? There have been so many people who have supported me unconditionally throughout this PhD journey. First, I want to dedicate this to my parents, Mike and Paige. They are my rocks and have been supportive of me in everything I do throughout my entire life. I would not be the woman I am today without their love, encouragement, and wisdom. Secondly, I want to dedicate this to my brother, Jakob. He has been such an inspiration to me over the past few months and has shown me what it means to be strong through adversity and never stop fighting for what you want and need. My sister, Jessica, also deserves a special dedication. She has been my roommate, my therapist, my friend, and everything in between. I am eternally grateful for her support. Finally, I want to dedicate this to my late grandparents, Bobby and Geraldine Fowler and Patty Farris, as well as my grandfather, Glendon Farris. They have each been such big influences in my life and in the research career and interests I have developed.

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my own projects. I feel confident that I can call both of you colleagues and friends. I am eager to stay in touch with you both and to continue working with you in the future.

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CANCER HISTORY IS RELATED TO NEUROLOGIC SPECIALTY CARE IN PATIENTS WITH DEMENTIA

LIST OF ABBREVIATIONS

ABCs	Alabama Brief Cognitive Screener
ACT	Adult Changes in Thought Study
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRD	Alzheimer's Disease and Related Dementias
ANOVA	Analysis of Variance
BMI	Body Mass Index
CNS	Central Nervous System
CRCI	Cancer-Related Cognitive Impairment
DBP	Diastolic Blood Pressure
ECHO	Extension for Community Healthcare Outcomes
EHR	Electronic Health Record
HR	Hazard Ratio
i2b2	Integrating Biology and the Bedside
ICD	International Classification of Disease
IPTW	Inverse Probability of Treatment Weighting
IRB	Institutional Review Board
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
NA	Not Applicable

NCI	National Cancer Institute
NDI	Neighborhood Deprivation Index
NHANES	National Health and Nutrition Examination Survey
NOS	Not Otherwise Specified
OR	Odds Ratio
SBP	Systolic Blood Pressure
SD	Standard Deviation
SNOMED	Systematized Nomenclature of Medicine Clinical Terms
UAB	University of Alabama at Birmingham
US	United States
95% CI	95% Confidence Interval

INTRODUCTION

Given that the risk for both cancer and dementia increases as individuals age,[1,2] cancer and dementia are known contributors to morbidity burden in adults 65 years and older. As the average age of the United States (US) population increases,[3] incidence and prevalence of both cancer and dementia are expected to increase.[4] Understanding the interplay between the two is crucial as cross-sectional studies have shown that there is an inverse relationship between the two conditions. Longitudinal studies can provide clearer evidence on this association and how it changes over time. This dissertation examines the longitudinal relationship between cancer history and cognition in dementia patients, how cancer treatments may influence this longitudinal relationship, and how care patterns differ in dementia patients based on cancer history. The following sections provide the epidemiology of cancer and dementia, rationale for the project, and project goals and aims. The subsequent sections of this document detail each aim as individual manuscripts.

Cancer Epidemiology

As of 2019, there were approximately 16.9 million individuals living with history of some form of cancer in the US, and more than 1.8 million incident cancer cases were expected in 2020.[1] Of these, the most common cancer types are that of the breast, prostate, colon / rectum, lung, urinary system, and skin.[1] Advancements in prevention,

screening, and treatment over the past several years have led to increased survival for many cancers.[1] With the exception of colorectal cancer, the five-year survival rate of the most common cancers range from 90-100%.[1] These high survival rates, coupled with increases in cancer incidence due to the increase in older adults, will ultimately lead to a greater number of people living longer after cancer, thus the need to understand how cancer and its treatments are related to other conditions of aging, such as cognitive decline/dementia.

All-Cause Dementia Epidemiology

In 2014, there were 5 million people living with Alzheimer's disease and related dementias (ADRD) in the US,[5] with almost all dementia cases being diagnosed in older adults.[2,5] The most common type of dementia is Alzheimer's disease (AD), representing 60-80% of cases.[2] However, evidence has shown that even in those with clinically diagnosed AD, many will have mixed pathologies at autopsy, including vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and more.[2] It is estimated that ADRD results in significant financial burden to the healthcare system with Medicare payments in 2019 at approximately $290 billion for those 65 and older. Financial burden also extends to caregiving with costs estimated at $234 billion.[2]

Racial and ethnic differences are pervasive across the ADRD spectrum. Black patients are especially more likely to present with mixed pathologies.[6-8] Black patients are also more likely to present with atypical (non-amnestic) AD, though this may be due to higher prevalence of cardiovascular disease in the Black population leading to a mixed vascular pathology.[9] Racial and ethnic minority groups are less likely to be included in clinical trials and non-pharmacologic studies of ADRD further perpetuating inequity of

information related to ADRD prevalence, incidence, diagnostics, and treatment between racial groups.[9] Finally, education and/or literacy may be lower in some racial and ethnic groups, which may affect the validity measures of cognitive testing used in these groups; however, very few studies have examined these effects.[9]

Cancer-Related Cognitive Impairment

Cognitive impairment is a known side effect of cancer and its treatments. Known as cancer-related cognitive impairment (CRCI), or colloquially as "chemobrain," this side effect results in impairment in many domains of cognitive functioning including memory, attention, and executive functioning.[10] Given its high prevalence and its relatively high long-term survival rate, most studies assessing CRCI have been conducted in breast cancer patients. Between 30-60% of breast cancer and other cancer patients report persistent long-term cognitive impairment after treatment completion.[10,11] Differences in the brains of breast cancer survivors have been found when compared to healthy adults of a similar age, including breast cancer patients using compensatory mechanisms to overcome working memory deficits, and having reduced activation in brain areas responsible for executive functioning compared to healthy patients.[12,13] Neuropsychological testing studies have further shown that breast cancer patients perform lower on tasks related to executive functioning and processing speed compared to healthy adults of a similar age.[14]

Cognitive Deficits Associated with Dementia

Like CRCI, dementia patients can experience impairment in memory, attention, and executive functioning with specific initial symptoms dependent upon the particular

underlying dementia syndrome.[2] In AD, patients present with memory deficits and mood disturbances with progression to deficits in attention and executive functioning.[2,15] Vascular dementia, however, presents with more executive functioning deficits such as the difficulty in making decisions and impaired judgment.[2,16] However, vascular dementia often presents concomitantly with other dementia syndromes.[2] Dementia with Lewy bodies is also often present concomitantly with AD, but initially presents with movement disturbances akin to Parkinson's disease, sleep difficulties, and visual hallucinations.[2] These symptoms can occur with or without impaired memory.[2] Given the prevalence of mixed pathologies and overlapping symptomology, it is therefore difficult to definitively know which pathology is present or dominant until autopsy.[2]

Shared Risk Factors Between Cancer and AD

The biggest risk factor for both cancer and dementia is age.[1,2] Other risk factors for cancer are smoking, cardiovascular disease, genetic risk factors, poor diet, physical inactivity, and increased body weight.[1] Similar risk factors are implicated in ADRD—especially in the two most common types of dementia, AD and vascular.[2] Due to shared risk factors and similar cognitive symptoms, it is logical to assume that cancer and dementia may be risk factors for each other. Yet, cross-sectional studies have indicated that there seems to be a mutually inverse relationship between the two diseases, where having one decreases risk of developing the other and vice versa.[17-20] In the Framingham Heart Study, a cohort of ~1500 White, older adults (approximately 60% female), it was found that cancer survivors were 10-24% less likely to develop AD compared to those without cancer history (Possible AD - HR: 0.90, 95% CI: 0.64-1.28; Probable AD - HR: 0.76, 95% CI: 0.52-1.12), and that those with AD were 71% less likely to develop cancer

(Possible AD - HR: 0.29, 95% CI: 0.17-0.49; Probable AD - HR: 0.29, 95% CI: 0.17-0.49). This effect was not fully accounted for by survival bias.[17] A meta-analysis of this association found a similar reduced risk of AD among those with cancer history (0.62, 95% CI: 0.53-0.74) and a reduced risk of cancer among those with AD (0.59, 95% CI: 0.42-0.82).[18] Studies in the population-based, prospective Adult Changes in Thought (ACT) study[19] and the population-based, prospective Rotterdam Study[20] further replicated these associations. Most of these studies have been conducted with only prevalent or incident AD, but one study examined this association longitudinally for incident AD or all-cause dementia and found a similar inverse association.[21]

Despite the apparent inverse relationship, anecdotal evidence of dementia in cancer survivors has been reported, but there are little data quantifying rates. A previous study by our group in participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal observational study of older adults with normal cognition, mild cognitive impairment (an early stage of the AD disease process), or AD, examined longitudinal progression of AD by self-reported cancer history status. This study indicated that in those with mild cognitive impairment, self-reported cancer history resulted in better cognitive function at baseline compared to those without self-reported cancer history, but there was no difference in rate of progression between the two self-reported cancer history groups.[22] We also noted that there was no difference in baseline cognition or rate of progression in those with AD at baseline.[22] These results seem to indicate that differences in cognition based on cancer history occur earlier in the AD disease process. However, since this study was conducted in an observational study of AD, participants were healthier, more likely to be White, and more highly educated, thus

justifying the need for a study using more representative and real-world patients. Additionally, this study was only able to utilize self-reported cancer history as the exposure, which may result in information bias, further justifying the need for a study utilizing objective measures of cancer history.

Cancer Treatment and Dementia

Several cancer treatments have been implicated in cognitive impairment.[23-40] As nicely summarized in a recent review article,[41] they reported that selective estrogen receptor modulators, a common type of hormone therapy used in breast cancer treatment, (e.g. tamoxifen) result in worse cognitive functioning.[28,31,32] They also report that aromatase inhibitors, another common hormone therapy used in breast cancer treatment, (e.g. letrozole) have mixed results on cognition.[26,28,32,33] Of note, these hormone therapies are typically used for several years following breast cancer remission.[41] Androgen-deprivation therapies, hormone therapies used in prostate cancer treatment, (e.g. leuprolide) are implicated in several indirect mechanisms of cognitive decline such as through depression, fatigue, cardiovascular disease, or low testosterone levels,[42-46] but direct studies of androgen-deprivation therapies on cognitive impairment have not produced consistent results.[35-41] Therapies targeted to specifically attack cancer cells can also induce cognitive side effects, but have not been studied extensively with respect to cognition.[41]

Other studies evaluating chemotherapies and cognition have found cognitive performance declines with increased chemotherapy duration,[47] and that for breast[48] and testicular cancers,[49] there may be a dose-response relationship resulting in worse cognitive performance with increased chemotherapy dosages.[10] Additionally,

Vannorsdall summarizes evidence suggesting some neurological dysfunction when exposed to certain chemotherapies used in multiple cancers such as methotrexate, 5-fluorouracil, cisplatin, and others.[10,50,51] Finally, it is mentioned that there is some mixed evidence for anthracycline-based chemotherapies being more neurologically harmful than non-anthracycline based chemotherapies.[10] Despite this treatment-related information, no studies have examined longitudinal associations between cancer treatment types and dementia progression specifically.

Guideline Care for Cancer Survival

Many cancer patients return to follow-up in primary care after remission. Unfortunately, in primary care, missed or delayed diagnosis of dementia is common.[52] This phenomenon has been thought to be a result of lack of training in dementia diagnosis for primary care physicians and patient / caregiver assumptions that cognitive decline is a result of normal aging and/or other comorbidities/medications.[52] Missed / delayed diagnosis in primary care along with prevalence of CRCI generates the questions of if, when, or why cancer patients may be referred to specialty care services. The American Cancer Society and the American Society of Clinical Oncology released guidelines for primary care follow-up of breast cancer patients.[53] It is recommended that primary care physicians should first ask cancer survivors if they are experiencing cognitive complaints, then should evaluate potential reversible causes of cognitive impairment and treat accordingly, and should finally refer for cognitive assessment and rehabilitation if indicated.[53] However, it is unknown whether these guidelines are being followed. Other guidelines for head and neck cancer,[54] prostate cancer,[55] and colorectal cancer[56] note that primary care physicians should follow cancer survivors for cognitive

dysfunction, but do not specifically note recommendations for referral to cognitive assessment by primary care physicians. To date, it is unclear if these guidelines are being followed justifying the need to examine specialty care utilization among dementia patients with and without cancer history.

Dissertation Project Goals and Aims

The overall goal of my dissertation is to expand upon the current literature examining the long-term trajectory of cancer survivors as they age and develop dementia. Specifically, I have constructed three objectives to reach this goal. Aim 1 will expand upon our previous study by evaluating cognitive progression in all-cause dementia patients who have survived cancer from a real-world clinic setting using the electronic health record (EHR) at a large academic medical center in the Southeast. Aim 2 will introduce new literature by examining the effect of cancer treatment types on dementia progression. Finally, Aim 3 will introduce new literature by evaluating the rate of specialty care service use in patients with and without cancer history. This objective will also serve the first to evaluate predictors of specialty care utilization. Each objective will be presented in the following sections as individual papers.

THE RELATIONSHIP BETWEEN PRIOR CANCER DIAGNOSIS AND ALL-CAUSE DEMENTIA PROGRESSION AMONG US ADULTS

by

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ABSTRACT

Background

Cancer-related cognitive impairment (CRCI) is a common effect of cancer and its treatments. Although CRCI and dementia syndromes, share common cognitive symptoms, cross-sectional studies demonstrate an inverse relationship between cancer and dementia. This study examines the longitudinal relationship between cognitive decline and cancer among a diverse sample, which has not been investigated.

Methods

Electronic health record data from July 2003 to February 2020 were extracted. Cognition and its decline were assessed using the Alabama Brief Cognitive Screener (ABCs). Adjusted linear mixed effects models were used to assess baseline cognition and rate of progression by prior cancer diagnosis. Effect modification by race was assessed.

Results

The study included 3,809 participants with dementia, of which 672 (17.6%) had cancer history. Those with any cancer history had higher baseline cognition (β: 0.62, 95% CI: -0.02-1.25), but declined similarly. However, those with cancers other than breast, prostate, colorectal, testicular, cervical, lung, and non-melanoma skin, had slower decline (β: 0.54, 95% CI: 0.10-0.97). There was significant interaction in the effect of cancer on cognition among dementia patients by race/ethnicity, with people of other race/ethnicity with cancer having sharper decline than those without.

Conclusions

In this retrospective cohort study, those with cancer history demonstrate better cognition at dementia diagnosis and no difference in cognitive decline than those with no cancer history. This is consistent with our prior analysis but expounds upon it by addressing important limitations. The current results indicate racial disparities between cancer survivors and non-survivors with dementia. Exploration of the causes is needed.

Keywords: Cancer-Related Cognitive Impairment; Dementia; Late Effects of Cancer; Aging

INTRODUCTION

Cancer and Alzheimer's disease (AD) are common aging-related diseases prevalent in adults aged 65 years and older. Specifically, approximately 1 in 8 males and 1 in 10 females will develop cancer from age 60-69,[1] and approximately 1 in 10 older adults has AD.[2] The prevalence of cancer and AD both increase with age, such that for those ≥70 years of age, approximately 1 in 3 males and 1 in 4 females will develop cancer,[1] and approximately 14% of those ≥71 years of age have dementia in general.[2] The United States (US) Census Bureau reports that by 2030, it is expected that 20% of the population will be 65 years and older (older adult).[3] This increase in the number of older adults will further increase prevalence of aging-related diseases, such as cancer and dementia. By 2025, it has been estimated that the proportion of the older adult population with AD (the most common form of dementia) is expected to increase by 40% from 2013.[4] Similarly, the proportion of cancer survivors will increase by 30% from 2010 to 2020.

Cancer and dementia share several common risk factors including age and vascular disorders.[2,5] Cancer and its treatments have also been shown to induce cognitive impairment similar to that experienced in dementia patients.[6-8] Given these findings, it might be assumed that cancer and dementia are risk factors for each other, but several cross-sectional studies have indicated a mutually inverse relationship between cancer and AD.[9,10] Other studies demonstrated a similar association between any cancer and

dementia in general.[11,12] Only one study has examined the association between cancer and AD or dementia longitudinally, and indicated a similar inverse association.[13] Further, a previous study from our group examined the association between cancer and longitudinal progression of AD, and concluded that those with self-reported cancer history demonstrated better cognition early in the AD disease course compared to those without self-reported cancer history, but the two groups experienced similar rates of cognitive decline.[14]

Our previous study was conducted using data from a longitudinal, observational study that included participants who were primarily White, healthy, and more highly educated. Additionally, the study used self-reported cancer history to determine cancer status.[14] Given the racial and ethnic disparities in AD,[15-18] it is unknown if these findings would apply in a more diverse cohort, particularly a cohort of real-world patients. Electronic health record (EHR) data allow access to real-world patient data, as well as the use of diagnostic and procedure codes to identify comorbidities of interest more reliably than self-report. The objective of this study is to examine the association between cancer and longitudinal progression of AD using data from the EHR from a large academic medical center in the Southeast.

METHODS

Study Population

Data for this study were obtained from the EHR at the University of Alabama at Birmingham (UAB), a large academic medical center. UAB houses the only National Cancer Institute (NCI) designated Comprehensive Cancer Center serving four states--

Alabama, Mississippi, Louisiana, and Arkansas. UAB also houses a Memory Disorders Clinic with neurologists and advanced-practice nurses specifically trained in diagnosing, treating, and researching all-cause dementia. Using the Informatics for Integrating Biology and the Bedside (i2b2) system,[19] EHR data from July 2003 to February 2020 were obtained. Patients were included if they met the following criteria: 1) had an International Classification of Disease (ICD)-10 or ICD-9 diagnosis code of all-cause dementia in any position on the diagnosis and/or problems list (see Supplemental Material for specific ICD-9 and ICD-10 codes), 2) had two or more cognitive test scores using the Alabama Brief Cognitive Screener (ABCs), and 3) 50 years old or older at the date of dementia diagnosis. Cancer exposed participants were additionally required to have an ICD-9/10 diagnosis code in any position on the diagnosis list, problems list, and/or the UAB tumor registry of non-central nervous system (CNS) cancer prior to dementia diagnosis (see Supplemental Material for specific cancer ICD-9/10 codes). The UAB tumor registry is a registry of all patients diagnosed with cancer at UAB. All Systematized Nomenclature of Medicine Clinical Terms (SNOMED) codes in the diagnosis and/or problems lists were converted to ICD-10 codes.

We conducted a chart review of 10% of the patients diagnosed with dementia, not otherwise specified (NOS) (ICD-9 codes: 290.0, 290.1x, 290.2x, 290.3, 290.9, 294.1x, 294.2x, 294.8, 331.2, 787; ICD-10 codes: F02.8x, F03.9x, F05, F06.0; F06.8; G31.1, R41.81, R41.9)[20] to verify pathology based on chart notes in order to ensure there was not additional information on dementia pathology. This study was approved by the UAB IRB.

Primary Outcome: Alabama Brief Cognitive Screener

The ABCs is a validated cognitive assessment tool developed by Geldmacher et al. to assess cognition in the clinic.[21-23] The assessment includes measures of orientation, memory, concentration, naming, and repetition. The ABCs has demonstrated good internal consistency (Chronbach's alpha=0.85).[24] The assessment tool also correlates well with the Mini Mental State Examination (MMSE).[25] Studies of the MMSE indicate a clinically significant difference of 1-3 points.[26] For this study, we will evaluate ABCs score at the time of dementia diagnosis, and change in ABCs score over time. The ABCs is typically performed every 6 months in the clinic.

Primary Exposure: Cancer Diagnosis History

The primary exposure was any cancer diagnosis prior to the dementia diagnosis using ICD-9/10 codes outlined in the Supplementary Material. Codes were searched from the problems list, diagnosis list, and the tumor registry. Those with CNS cancers were excluded due to the potential for negative cognitive consequences related to CNS tumors and the inability to extrapolate CRCI from brain tumor induced cognitive impairment. An all-cancer category was created excluding non-melanoma skin cancer. The following specific cancer variables were created: breast, prostate, colorectal, non-melanoma skin, testicular, cervical, lung, and all other cancers. A separate variable was also created for those with two or more cancers.

Covariates

Demographics, Health Behaviors, and Socioeconomic Factors. Demographic information was collected on the dementia diagnosis date including the following: age at

dementia diagnosis, race, ethnicity, sex, and marital status. Race and ethnicity were combined to create a categorical variable with three levels: non-Hispanic White, non-Hispanic Black, and other. Smoking status was collected at some visits as a free-text variable. The smoking status on or closest to dementia diagnosis was used to categorize participants as 'ever' or 'never' smoker based on the free-text responses. Closest height and weight within 12 months of the dementia diagnosis were used to calculate body mass index (BMI). BMI values were evaluated and for values which were impossible or inconsistent with other visits, the value next closest to the dementia diagnosis was used. For socioeconomic status, the Neighborhood Deprivation Index (NDI) was created using previously documented methodology by Ross et al.[27] Briefly, ZIP codes at dementia diagnosis were collected and merged with county FIPS codes to create 9-digit ZIP codes. The 9-digit ZIP code was merged with data on percentage of female-headed households and percentage of households below the poverty line. These data were obtained from the American Community Survey 5-year estimates from 2019, which extrapolates back to 2015. From there, the percentage of female-headed households and percentage of households below the poverty line were each divided by 10, and the mean of the two variables were calculated to create the NDI score for each participant's 9-digit ZIP code area. Ross and Mirowsky note in another study that ZIP codes are the "next best approximation to a neighborhood" if census tracts are unavailable as in the EHR.[28] The ABCs began consistent use in the Memory Disorders Clinic in 2013 so most dementia diagnoses were documented between 2013 and 2019, overlapping with the underlying data used to calculate the NDI score. NDI was divided into quartiles for stratified models.

Insurance status at dementia diagnosis was also collected and collapsed into categories of private, government, and other insurance.

Comorbidities. Depression was determined based on diagnosis codes and medications using the algorithm of Trinh et al.[29] Specific ICD-9/10 codes (Supplementary Material) were identified from the diagnosis list or problems list for each participant on or at any time prior to the dementia diagnosis. Medications for depression (Supplementary Material) were identified from the medication list on or at any time prior to the dementia diagnosis. Participants with either a depression diagnosis or a medication for depression were classified as having depression. Those with neither depression diagnosis codes nor medications were classified as not having depression.

A vascular propensity score was created to adjust for vascular risk factors.[30-32] In the current analysis, logistic regression was used to determine the probability of having cancer (using the all-cancer group) with smoking status, diabetes status, hypertension status, and BMI as predictors. Participants missing any vascular predictors were excluded from the model. Diabetes status was determined based on ICD-9/10 codes on the diagnosis list and problems list on or at any time prior to dementia diagnosis, diabetic medications on or at any time prior to dementia diagnosis (specific codes and medications listed in the Supplementary Material), and glucose levels at dementia diagnosis. Those with a glucose of $\geq$ 200 mg/dL, positive for a diagnosis code, and/or positive for a medication were classified as having diabetes. Those with glucose levels below the threshold, without any diagnosis codes, and without medications were classified as not having diabetes. Hypertension status was determined in a similar manner. Systolic and diastolic blood pressure levels on or closest to the dementia

diagnosis and ± 12 months were used for vitals-based hypertension categorization. Extreme values were compared to other visits and if impossible or inconsistent with other visits, the next closest value was taken. Participants were considered to have hypertension based on blood pressure levels if systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Participants who were positive for hypertension on systolic / diastolic blood pressure level, diagnosis code, and/or medications were classified as having hypertension. Again, participants without all criteria were classified as not having hypertension. This multi-level approach of diagnosis codes and medications is often used in classification of chronic conditions in studies utilizing administrative claims-based data.[33]

Anticholinergic Burden. Medications considered to have anticholinergic activity have been associated with dementia risk and cognitive impairment.[34,35] Anticholinergic burden was calculated using the algorithm with of Boustani et al.[35] Briefly, anticholinergic score was assigned to individual medications on or at any time prior to before dementia diagnosis, and the score was totaled for each participant to determine overall anticholinergic score on dementia diagnosis. A clinically significant anticholinergic burden is a total score of ≥ 3. The anticholinergic scale is the most widely used anticholinergic burden scale, having been used in several studies to predict cognitive impairment, and compares well to other anticholinergic burden scales.[36]

Dementia-Related Medications. Medications for dementia are designed to slow cognitive decline in mild to moderate dementia patients. A dementia medication variable was created by searching each participant's medication list on or after the dementia diagnosis. If participants were prescribed donepezil (Aricept), galantamine (Razadyne),

rivastigmine (Exelon), memantine (Namenda), and/or donepezil + memantine (Namzaric), they were classified as taking a dementia medication on or after the dementia diagnosis.

Statistical Analysis

Differences in participant characteristics were examined between those with and without cancer history using chi-square tests and t-tests for categorical and continuous variables, respectively. Fisher's exact tests were used where expected sample size was insufficient for categorical variables. Hierarchical linear mixed effects models with a random effect for time were used to assess differences in baseline cognition and cognitive progression among cancer groups.[37] First, models were adjusted for basic demographics including: age at dementia diagnosis, race, and sex. Next, the model was further adjusted for other socioeconomic variables (NDI and insurance status). The final model was fit further adjusting for anticholinergic burden, depression, vascular propensity score, and dementia medication use. The results of the models included the intercept (or the main effect of cancer), which describes the difference in baseline cognitive score based on cancer history status and the slope (or the cancer by time effect), which describes the difference in cognitive decline over time based on cancer history status. Separate sets of models were performed for specific cancer groups with sufficient sample size (n = 20). Tests for interaction by race and NDI were assessed to evaluate if these variables modified the association in baseline cognition and cognitive progression by cancer history status for the all-cancer group and other cancer group. Models were stratified by the effect modifying variable if significant interactions were found. Statistical

significance was set at $\alpha=0.05$ and analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC) and RStudio 1.2.5033.

RESULTS

The study sample included 3,809 participants with dementia, of which 672 (17.6%) and 3,137 (82.4%) did and did not have a history of cancer, respectively. Of the 672 with a history of any cancer not including non-melanoma skin cancer, 29 (4.3%) had a history of only colorectal cancer, 66 (9.8%) had a history of only breast cancer, 16 (2.4%) had a history of only lung cancer, 65 (9.7%) had a history of only prostate cancer, 356 (53.0%) had a history of other cancers, and 139 (20.7%) had a history of two or more cancers (Figure 1).

There were 53 (1.4%) of the total sample with only non-melanoma skin cancer (Figure 1). Those with a history of any cancer were significantly older (76.4 vs. 73.2, p: <0.0002), more likely to be widowed (26.2% vs. 20.7%, p: 0.0266), had lower NDI score (0.79 vs. 0.84, p: 0.0364), more likely to be on a government insurance plan (90.5% vs. 84.7%, p: 0.0005), and more likely to be an ever smoker (47.1% vs. 42.9%, p: 0.0461) than those without a history of cancer (Table 1). Patients with a history of cancer also had a significantly lower mean diastolic blood pressure (73.9 vs. 75.1 mmHg, p: 0.0101), were more likely to have depression (72.2% vs. 68.9%, p: <0.0001), hypertension (89.3% vs. 81.4%, p: <0.0001), and diabetes (33.3% vs. 24.9%, p: <0.0001), have higher mean total anticholinergic burden (6.9 vs. 3.8, p: <0.0001) and vascular propensity scores (0.19 vs. 0.17, p: <0.0001), and were less likely to be on a dementia medication (57.4 vs. 62.1, p: 0.0255) than those without a history of cancer (Table 1).

Dementia codes differed by cancer history (AD: 17.6% vs. 22.9%; Alcohol-induced: 0.3% vs. 0.2%; Dementia with Lewy Bodies: 2.5% vs. 4.0; Frontotemporal: 2.2% vs. 4.2%; Vascular: 6.7% vs. 6.1%; Not otherwise specified: 70.4% vs. 62.6%; Other: 0.3% vs. 0.0%; p-value: <0.0001). Dementia, NOS was the most common code in each group, though there was a larger proportion of Dementia NOS in patients with a history of cancer than those without (70.4% vs. 62.6%). The proportion of AD was slightly lower in those with a history of cancer than those without (17.6% vs. 22.9%) (Table 1). Of the participants with dementia, NOS, a 10% sample was chart-reviewed for specific pathology. Of these, 74 (27.4%) had AD, 63 (23.3%) had pathology still unable to be identified, and 133 (49.3%) had dementia of another pathology (Vascular, Parkinson's-related, Dementia with Lewy Bodies, mixed, etc.), thus potentially increasing the overall prevalence of each specific dementia type. The prevalence of each dementia subtype is likely an underestimate.

Effects of cancer history on baseline cognition and cognitive progression

The initial model adjusted for age at dementia diagnosis, race, and sex revealed that those with any cancer history began with cognition 1.51 (95% CI: 0.94-2.08) points higher as measured by the ABCs and progressed 0.41 (95% CI: 0.11-0.71) points per year slower than those without any cancer history (Table 2). When examining by cancer site, no significant results were indicated for baseline cognition or cognitive progression with exception of those with history of other cancers. Those with history of other cancers (not including colorectal, breast, prostate, testis, cervix, and lung), began with baseline cognition 1.66 (95% CI: 0.91-2.41) points higher and progressed 0.62 (95% CI: 0.22-1.01) points per year slower than those without cancer history. Finally, those with history

of two or more cancers began with baseline cognition 2.05 (95% CI: 0.87-3.23) points higher than those without cancer history (Table 2).

After adjustment for socioeconomic factors of NDI and insurance status, results remained relatively unchanged. Those with any cancer history began with cognition 1.49 (95% CI: 0.91-2.07) points higher and progressed 0.40 (95% CI: 0.08-0.71) points per year slower than those without any cancer history (Table 2). Evaluating by cancer site maintained non-significant results for both baseline cognition and cognitive progression with exception of those with history of other cancers. Those with history of other cancers began with baseline cognition 1.63 (95% CI: 0.87-2.40) points higher and progressed 0.63 (95% CI: 0.22-1.04) points per year slower than those without cancer history. Similar to the initial model, those with history of two or more cancers began with baseline cognition 2.21 (95% CI: 1.03-3.40) points higher than those without cancer history (Table 2).

Results significantly attenuated after further adjustment for total anticholinergic burden, vascular propensity score, depression, and dementia medication. Those with any cancer history began with cognition 0.62 (95% CI: -0.02-1.25) points higher and progressed 0.26 (95% CI: -0.07-0.59) points per year slower than those without any cancer, so these results were no longer significant [Table 2]. When evaluating by cancer site, again no significant results were observed with exception of the other cancer group. Those with history of other cancers began with non-significant baseline cognition 0.56 (95% CI: -0.26-1.39) points higher, but progressed significantly 0.54 (95% CI: 0.10-0.97) points per year slower than those with no cancer history [Table 2]. Finally, for those with history of two or more cancers, results were not significant, but exhibited a similar

pattern compared to the prior models where those with history of 2 or more cancers began 0.97 (95% CI: -0.32-2.25) points higher and progressed 0.31 (95% CI: -0.31-0.93) points per year slower than those without cancer history [Table 2]. Figure 2 depicts the predicted baseline score and progression over time for each cancer group compared to the no cancer group.

Tests for interaction by race and NDI in the all-cancer model were significant (race: p-value=0.0299, NDI: p-value: 0.0222) and tests for interaction by race and NDI in the other cancer model were also significant (race: p-value=0.0408, NDI: p-value=0.0342). Stratified models by cancer status showed that regardless of cancer status non-Hispanic Blacks and non-Hispanic Whites are similar at baseline and over time, but those with other races and cancer declined faster (Figure 3). Stratified models by cancer status were also conducted for NDI, with quartile 1 representing NDI ≤ 0.42 and quartile 4 representing NDI greater than 1.07 (Figure 4). All NDI quartiles demonstrated similar baseline cognitive impairment and rates of progression. Stratified models by cancer with respect to race and NDI were also conducted and results were similar to those seen in the stratified models for all cancers (Figure 5, Figure 6). Although the overall NDI interaction term p-value was significant for both the any cancer and other cancer models, when stratifying, we did not see any significant effect modification by cancer status.

DISCUSSION

This analysis of EHR data from a large academic medical center in the Southeast US revealed an approximate 0.5-point higher cognitive score at baseline (intercept) and an approximate 0.5-point slower decline (slope) in cognitive score for those with any cancer history compared to those without cancer history. Due to small sample size in

each group, these results did not hold for specific cancers individually with exception of those with other cancers (other than breast, lung, colorectal, prostate, testis, cervix, and non-melanoma skin). Additionally, for those with two or more cancers, the baseline results were consistent but not significant, and cognitive decline results were not significant. Results among those with any cancer should be interpreted with caution given potential heterogeneity in different cancer types. However, the results for the group with other cancers and two or more cancers were similar to that of the any cancer group and the inconsistent results in the remaining specific cancer groups may be due to relatively small sample size in these groups. Furthermore, race/ethnicity and socioeconomic status modified the relationship between cancer history and cognition / cognitive progression with non-Hispanic Blacks beginning at a lower baseline cognitive score and maintaining this difference throughout follow-up, and those in higher quartiles of NDI (i.e. more disadvantaged) beginning at a higher baseline cognitive score and maintaining this difference throughout follow-up.

These results are consistent with those from our prior work in the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset.[14] Specifically, our prior study indicated clinically significant better baseline cognition but no difference in slope in those with self-reported cancer history compared to those without self-reported cancer history. This effect was only seen in those with mild cognitive impairment (MCI), but not AD. The current study also reveals significant better baseline cognition for those with a previous cancer diagnosis compared to those without a previous cancer diagnosis. However, in contrast to the prior study, this effect was seen in those with dementia and not strictly MCI.

The findings from this current study correspond to results from our prior analysis, but extend the previous study by addressing many of the prior study's important limitations.[14] In the current study, cancer exposure is based on actual diagnoses and not simply based on self-report, minimizing information bias. This analysis also included a more racially and socioeconomically diverse sample, with ~20% of the sample being non-Hispanic Black, and approximately 10% prevalence of households under the poverty line or single-mother households in the ZIP code. In addition, the study sample includes less healthy individuals with ~70% having depression, ~80% having hypertension, ~30% having diabetes, high mean total anticholinergic burden score, and ~50% of the sample being ever smokers. The inclusion of a more representative sample improves generalizability and helps alleviate concerns of selection bias driving the results. Additionally, this is an unselected clinic sample using the EHR. Previous studies have shown that approximately 75% of AD patients in the clinic are not eligible for clinical trials or observational studies, further improving generalizability of the current sample.[38,39]

Results from this study do differ from the previous analysis in that this study was conducted in all-cause dementia patients rather than in AD patients specifically. Unfortunately, coding of AD and specific dementia codes in the EHR is imperfect and recorded as a non-specific all-cause dementia code.[40] This was further corroborated in the UAB EHR according to physicians in the UAB Memory Disorders Clinic. However, previous studies have also demonstrated an inverse cross-sectional relationship in all-cause dementia making the current results commensurate with studies assessing AD specifically.[11,12] The previous analysis indicated that the differences seen between cancer

exposed and cancer non-exposed began earlier and in the MCI stage,[14] but the current analysis identifies patients in the dementia stage rather than at the MCI stage and contradicts the previous results. This effect may be due to a more diverse sample of real-world patients or a more cognitively diminished sample of patients rather than those willing and able to enroll in an AD observational study. The current sample did include a majority with dementia, NOS, potentially driving the results. After chart review, approximately 23% of these remained with no discernable pathology. However, this is less of a concern as these participants are still diagnosed in the dementia stage and not the MCI stage. MCI has its own distinct diagnosis code, which is used for individuals with cognitive impairment not yet severe enough to be considered a true dementia syndrome. This does not necessarily suggest that MCI would be appropriately diagnosed, but one study indicated that neurologists frequently see patients with MCI preferentially utilize this diagnostic code for patients with mild cognitive decline. [41]

It is important to note the clinical significance of these results. The ABCs has been correlated with scoring on the MMSE.[25] The minimally clinically important difference on the MMSE has been studied and determined to be approximately 1-3 points.[26] In the current analysis, we observed an approximate 0.5-point difference in baseline cognition on the ABCs between those with and without cancer history, indicating that having had cancer results in somewhat improved cognition at dementia diagnosis but this may not necessarily be clinically significant. Consistent with prior results, the rate of decline was also not clinically significant and showed varying results based on cancer type. Furthermore, it appears that risk factors and comorbidities play a role in attenuating the association. Prior to adjustment for these confounders, we

observed approximately 1.5 to 2-point higher baseline cognitive score and 0.5-point slower cognitive progression between those with and without cancer history. Investigation into the role of certain comorbidities and smoking on cognition after cancer is necessary to elucidate mechanisms of this attenuation and to identify areas for intervention. Additionally, results among those with any cancer should be interpreted with caution given potential heterogeneity in different cancer types.

Known racial and ethnic differences exist in cancer[42-44] and dementia.[15-18] These results are noted in this study as well. It appears that those with races other than non-Hispanic White and non-Hispanic Black and cancer history decline faster than non-Hispanic Blacks and non-Hispanic Whites with cancer history, but in those without cancer history the same effect was not seen. Furthermore, it seems that those with cancer history begin higher at baseline than those without cancer history which is maintained throughout follow-up, regardless of race. The absolute difference between cognitive scores at baseline by cancer history status should be further evaluated with respect to race. It also appears that there is no difference in baseline cognitive score or progression over time based on NDI status regardless of cancer status. However, those with cancer history again begin at a higher baseline cognitive score compared to those without cancer history. This higher score is maintained throughout the follow-up period. Those in higher quartiles represent ZIP codes with higher rates of poverty and female-headed households compared to those in lower quartiles. Therefore, it seems more likely that participants from more disadvantaged backgrounds would begin at a lower baseline cognitive score than those in lower quartiles.[45,46] However, due to lack of broad heterogeneity in the sample's NDI, these results may not be consistent in a more geographically diverse

sample. Again, the absolute difference between cognitive scores at baseline by cancer history status should be further evaluated with respect to NDI.

Exploration of the potential causes of these effects is necessary. The general effect could be due to differing cancer treatments, improved social support in cancer survivors, or increased access to the healthcare system following cancer diagnosis and treatment. Kelly et al. conducted a systematic review assessing social support in healthy older adults and concluded that increased social activity, larger social networks, and improved social support result in better cognition.[47] Other studies have indicated that satisfaction with social support,[48] social networks and quality of these networks,[49] and level of social support[50] offer improved cancer-related outcomes. The American Cancer Society has released Survivorship Care Guidelines for colorectal,[51] breast,[52] prostate,[53] and head / neck cancer,[54] and in each of these guidelines indicate the need for a history and physical and assessment of long-term / late psychosocial effects of these cancers routinely throughout the first year after treatment completion. With these routine examinations, primary care physicians may be more likely to catch dementia syndromes early. However, diagnosis of dementia is notoriously missed or delayed in primary care settings,[55] but since patients had prior cancer the primary care physicians may be more aware of cognitive issues.

These results support the need for further exploration of potential racial and/or geographic disparities of these associations given known access to care disparities[56-58], cancer disparities among racial and geographic groups,[42,43,59-61] and dementia disparities among racial and geographic groups.[18,62] Delving deeper into the difference in cognitive performance by cancer history and race could lead to interventions to improve cognitive

performance in disadvantaged groups, specifically if they are unique to cancer survivors and not general factors associated with disparities in cognition. Exploration of the general associations and the racial interaction in a larger sample of specific cancer types is also necessary as specific cancer types may have differing mechanisms of cognitive impairment and lead to specific strategies for survivors of certain cancers especially in certain racial groups. Given the NDI results, this should also be evaluated in a more heterogeneous sample.. Many of the participants in this study lived in ZIP codes in Alabama and around the Birmingham area. The homogeneity of this sample may have, therefore, led to the observed trends.

This study has several strengths. First, it examines the association between cancer and dementia progression in a more externally representative population with decreased likelihood of selection bias. Additionally, these participants came from an ambulatory clinic population so external validity also includes individuals seeking care for dementia rather than those willing to enroll in an AD observational study. Secondly, it utilizes diagnosed cancer rather than self-reported cancer history reducing information bias. This study was also able to assess several potential confounders such as comorbidities, anti-cholinergic burden, and cardiovascular risk factors which limits the possibility of residual confounding. This study examined individuals at the dementia stage rather than at early, mild stages of impairment, which expands upon our prior analysis. This study was also able to examine interaction by important racial and socioeconomic variables.

Despite its strengths, this study is not without limitations. First, cancer patients may have received many different treatments, but many did not have complete cancer treatment information. Some diagnoses came from the problem list where non-oncology

physicians recorded the diagnosis, but these patients had received treatment outside UAB so treatment information was not recorded. An additional analysis is planned to assess specifics of cancer treatment on dementia progression in this sample. Secondly, some participants may have been on dementia-related medications prior to dementia diagnosis, as they may be prescribed earlier in the disease process. However, these medications usually continue into the dementia stage. It was not possible to know the specific type of dementia for each participant. Frequently, these dementias are billed as dementia NOS, rather than the specific pathology. The chart review does alleviate some of these concerns because most of the 10% review sample diagnosed with dementia, NOS had specific pathologies noted in their chart notes. Despite about 23% still not having discernable pathology listed, it is not expected that this would alter results as these participants were diagnosed with a dementia syndrome. Also, identification of BMI was not perfect as many were not performed on the dementia diagnosis date. We restricted measurements to within one year of diagnosis to minimize this limitation, similar to the one-year baseline for identification of comorbidities used in administrative claims-based studies.[63,64] Identification of smoking was also imperfect as many were not performed on the dementia diagnosis date and many were greater than one year out from the diagnosis date. However, smoking categorization was as ever or never smoker. It is not expected that an older adult would take up smoking late in life. Some individuals in the other cancer group may have had two or more other types of cancer. Finally, cancer diagnoses or diagnoses of comorbidities could have been missed due to lack of documentation in the diagnosis list, problem list, or tumor registry resulting in information bias. However, this would bias results toward the null. It is expected that those seen and treated at UAB

were present in the diagnosis list and/or tumor registry, but those who received cancer care outside UAB may not have been documented in the record.

CONCLUSION

CRCI can have negative effects on patients' well-being, but the longitudinal association between CRCI and dementia progression has been under studied. Expanding on our previous work, we found that baseline cognition is significantly higher and cognition declines slower in those with a history of cancer compared to those who do not. These results were marginally clinically significant and it appears that smoking and comorbidities play a role in attenuating the association. Further explorations on the reasons for this underlying association are needed, such as studies including more socioeconomic variables / geographic variability, information on cancer staging and death information for competing risk, and larger samples of specific cancer types.

Table 1. Participant Characteristics by Cancer History Status.[*]

	Cancer (n=672)	No Cancer (n=3137)	p-value
Demographics			
Age at Dementia Diagnosis	76.4 ± 8.9	73.2 ± 9.7	**<0.0001**
Sex			0.2097
Male	294 (43.8)	1290 (41.1)	
Female	378 (56.3)	1847 (58.9)	
Race			**<0.0001**
Non-Hispanic White	510 (75.9)	2147 (69.5)	
Non-Hispanic Black	123 (18.3)	516 (16.7)	
Other	39 (5.8)	428 (13.8)	
Marital Status			**0.0266**
Married	369 (56.6)	1554 (58.8)	
Divorced	48 (7.4)	211 (8.0)	
Single	60 (9.2)	306 (11.6)	
Widowed	171 (26.2)	548 (20.7)	
Other	4 (0.6)	23 (0.9)	
NDI[†]	0.79 ± 0.54	0.84 ± 0.52	**0.0364**
Insurance Status			**0.0005**
Private	58 (8.9)	422 (14.0)	
Government	589 (90.5)	2548 (84.7)	
Other	4 (0.6)	40 (1.3)	
Health Variables			
Smoking			**0.0461**
Ever	315 (47.1)	1335 (42.9)	
Never	354 (52.9)	1779 (57.1)	
BMI (kg/m^2)[†]	26.6 ± 5.8	26.8 ± 5.6	0.3764
SBP (mmHg)[†]	133.9 ± 21.3	135.3 ± 21.2	0.1380
DBP (mmHg)[†]	73.9 ± 10.7	75.1 ± 10.6	**0.0101**
Glucose Level (mg/dL)[†]	121.4 ± 58.1	117.5 ± 54.9	0.2268
Depression[†]			**<0.0001**
Yes	421 (72.2)	1447 (68.9)	
No	162 (27.8)	1009 (41.1)	
Dementia Categories			**<0.0001**
Alzheimer's Disease	118 (17.6)	717 (22.9)	
Alcohol-induced	2 (0.3)	7 (0.2)	
Dementia with Lewy Bodies	17 (2.5)	125 (4.0)	
Frontotemporal	15 (2.2)	131 (4.2)	
Vascular	45 (6.7)	192 (6.1)	
Not otherwise specified	473 (70.4)	1965 (62.6)	
Other[‡]	2 (0.3)	0 (0.0)	
Dementia Medication[†]			**0.0255**
Yes	386 (57.4)	1947 (62.1)	
No	286 (42.6)	1190 (37.9)	
Hypertension[†]			**<0.0001**

Yes	600 (89.3)	2547 (81.4)	
No	72 (10.7)	583 (18.6)	
Diabetes[†]			**<0.0001**
Yes	224 (33.3)	780 (24.9)	
No	448 (66.7)	2350 (75.1)	
Total Anticholinergic Burden[†]	6.9 ± 6.4	3.8 ± 4.8	**<0.0001**
Vascular Propensity Score[†]	0.19 ± 0.04	0.17 ± 0.04	**<0.0001**

[*]Cancer +: participants with any cancer excluding cancers of the central nervous system and non-melanoma skin cancer. Cancer -: participants without any cancer, but may have non-melanoma skin cancer. Evaluated using t-tests and chi-square tests / Fisher's exact tests (where necessary) for continuous and categorical variables, respectively. Significance set at α=0.05

[†]NDI: neighborhood deprivation index based on algorithm published by Ross et al.[27,28]; BMI: body mass index calculated using height / weight closest to dementia diagnosis within 1 year of diagnosis; SBP: systolic blood pressure, on or closest to dementia diagnosis within 1 year of diagnosis; DBP: diastolic blood pressure, on or closest to dementia diagnosis within 1 year of diagnosis; glucose level: on or closest to dementia diagnosis within 1 year of diagnosis; depression: based on algorithm published by Trinh et al.[29]; dementia medication: donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), memantine (Namenda), and/or donepezil + memantine (Namzaric); hypertension: based on SBP $\geq$ 140 mmHg / DBP $\geq$ 90 mmHg, diagnosis of hypertension prior to dementia diagnosis, and/or presence of hypertensive medications prior to dementia diagnosis; diabetes: based on glucose of $\geq$ 200 mg/dL, diagnosis of diabetes prior to dementia diagnosis, and/or presence of diabetic medications prior to dementia diagnosis; total anticholinergic burden: prior to dementia diagnosis based on algorithm published by Boustani et al.[35]; vascular propensity score: propensity of cancer exposure based on smoking status, BMI, hypertension status, and diabetes status

[‡]Other includes Creutzfeldt-Jakob disease, Huntington's disease, drug-induced dementia

Table 2. Estimates of Cognitive Performance at Baseline and Decline Over Time by Cancer History Status*

	Model 1†	Model 2¥	Model 3**
	β (95% CI)	**β (95% CI)**	**β (95% CI)**
All Cancer			
Intercept	**1.51 (0.94-2.08)**	**1.49 (0.91-2.07)**	0.62 (-0.02-1.25)
Slope	**0.41 (0.11-0.71)**	**0.40 (0.08-0.71)**	0.26 (-0.07-0.59)
Non-Melanoma Skin Cancer‡			
Intercept	0.46 (-1.35-2.27)	0.28 (-1.55-2.10)	-0.06 (-1.98-1.85)
Slope	-0.44 (-1.41-0.54)	-0.33 (-1.33-0.67)	-0.66 (-1.69-0.38)
Colorectal Cancer			
Intercept	0.96 (-1.60-3.53)	0.67 (-1.98-3.31)	-0.18 (-3.03-2.67)
Slope	0.27 (-1.16-1.70)	0.44 (-1.06-1.94)	0.43 (-1.19-2.06)
Breast Cancer			
Intercept	-0.18 (-1.84-1.48)	-0.50 (-2.00-1.40)	-0.83 (-2.67-1.01)
Slope	-0.34 (-1.27-0.59)	-0.43 (-1.41-0.56)	-0.66 (-1.69-0.37)
Prostate Cancer			
Intercept	1.62 (-0.01-3.25)	1.50 (-0.17-3.17)	1.63 (-0.12-3.39)
Slope	-0.36 (-1.29-0.57)	-0.50 (-1.48-0.48)	-0.76 (-1.73-0.21)
Other Cancers			
Intercept	**1.66 (0.91-2.41)**	**1.63 (0.87-2.40)**	0.56 (-0.26-1.39)
Slope	**0.62 (0.22-1.01)**	**0.63 (0.22-1.04)**	**0.54 (0.10-0.97)**
Two or More Cancers			
Intercept	**2.05 (0.87-3.23)**	**2.21 (1.03-3.40)**	0.97 (-0.32-2.25)
Slope	0.46 (-0.12-1.04)	0.39 (-0.20-0.98)	0.31 (-0.31-0.93)

*Estimated using linear mixed effects models with a random effect for time. Cognition measured using the Alabama Brief Cognitive Screener (ABCs). Significance set at α=0.05. Intercept indicates the mean difference in ABCs score based on cancer status; slope indicates the mean difference in decline on the ABCs per year based on cancer status.

†Adjusted for sex, race, and age at dementia diagnosis

‡Non-melanoma skin cancer patients may have other cancers as well

¥Adjusted for all variables in Model 1 plus neighborhood deprivation index and insurance status

**Adjusted for all variables in Model 2 plus total anti-cholinergic burden before dementia diagnosis, vascular propensity score on or before dementia diagnosis, depression status on or before dementia diagnosis, and taking a dementia medication on or before dementia diagnosis

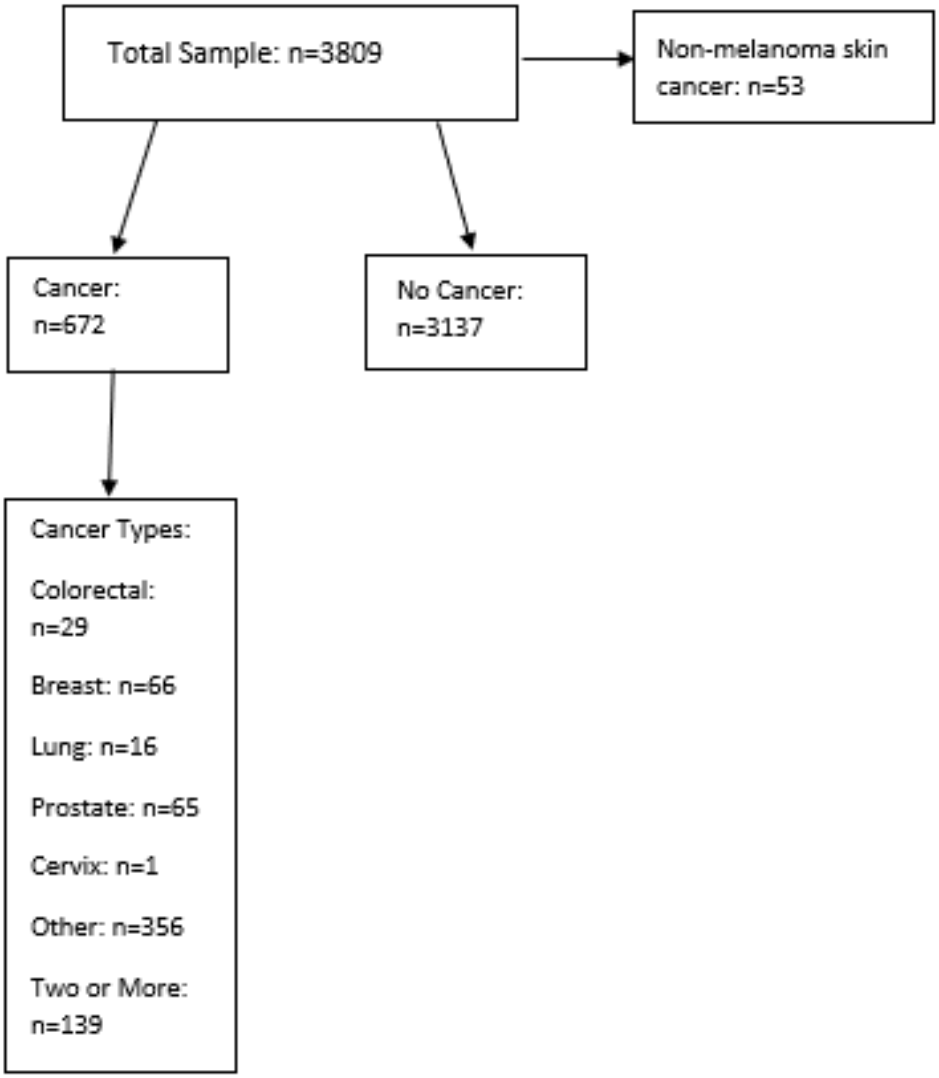

Figure 1. Flow Chart of Participant Categorization. Those with only history of non-melanoma skin cancer were not included in the cancer group.

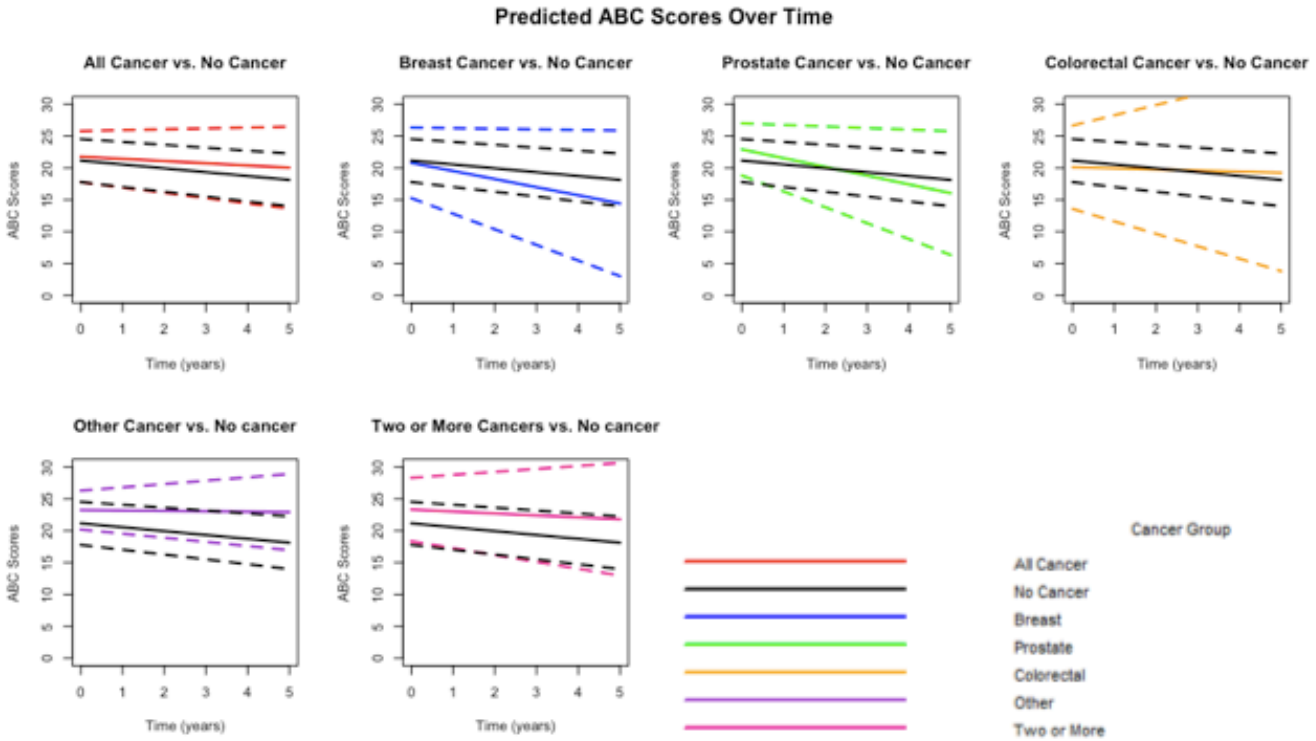

Figure 2. Predicted Alabama Brief Cognitive Screener (ABCs) Scores Over Time by Cancer History Group. Dementia patients with history of any cancer (excluding those with central nervous system cancers or only non-melanoma skin cancer) demonstrate better baseline cognitive score and slower decline over time compared to the dementia patients in the group with no cancer history. Similar associations are seen for those with history of other cancers and two or more cancers.

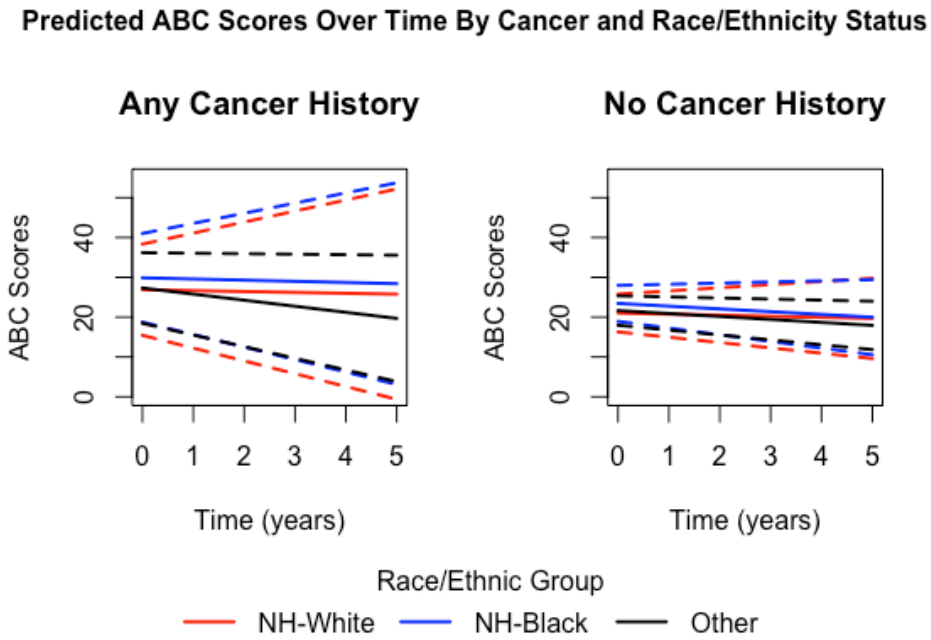

Figure 3. Predicted Alabama Brief Cognitive Screener (ABCs) Scores Over Time by Race Group in Those with Any Cancer History. Non-Hispanic Black dementia patients with history of any cancer (excluding those with central nervous system cancers or only non-melanoma skin cancer) and Non-Hispanic White dementia patients with history of any cancer demonstrate similar cognitive impairment at baseline and progress similarly, but those of Other races demonstrate faster decline. Similar cognitive impairment at baseline and rates of progression are seen for those without cancer history regardless of race. However, those without cancer history demonstrated lower cognition at baseline compared to those with any cancer history.

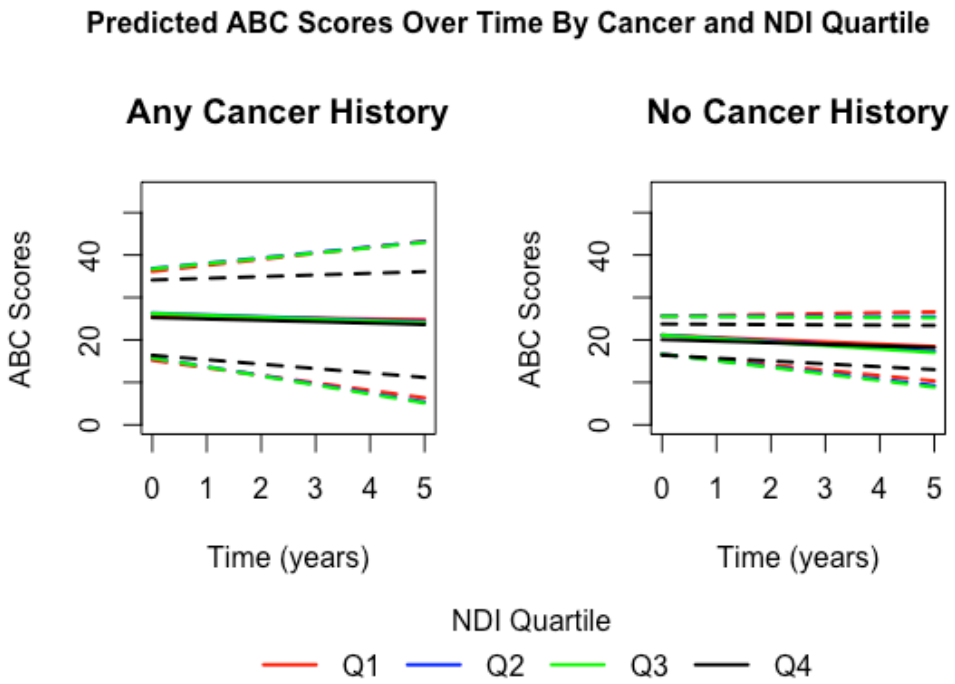

Figure 4. Predicted Alabama Brief Cognitive Screener (ABCs) Scores Over Time by NDI Quartiles in Those with Any Cancer History. Dementia patients (excluding those with central nervous system cancers or only non-melanoma skin cancer) have similar baseline cognitive impairment and rate of decline regardless of neighborhood deprivation status. However, those with no cancer history seem to begin with lower cognition at baseline compared to those with any cancer history.

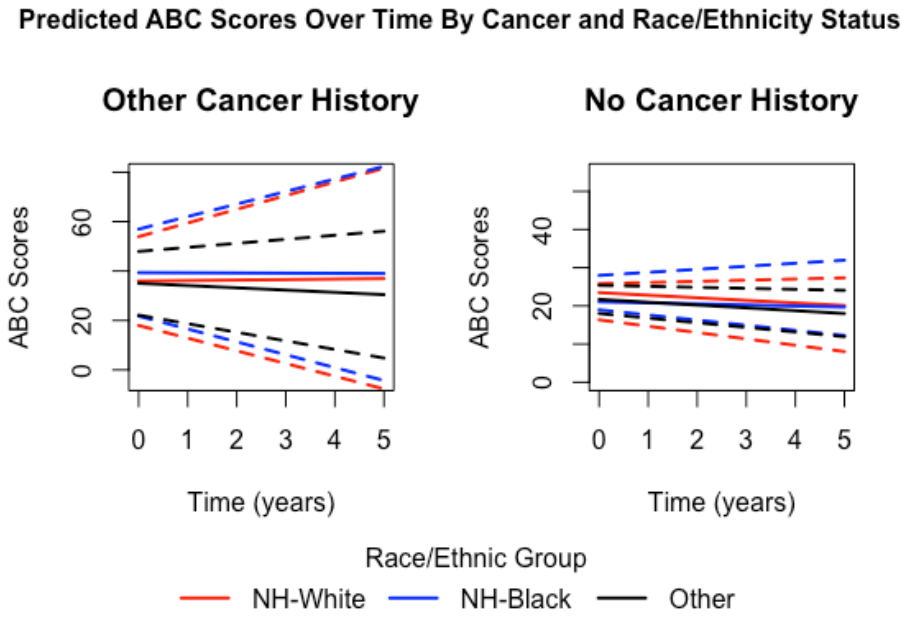

Figure 5. Predicted Alabama Brief Cognitive Screener (ABCs) Scores Over Time by Race Group in Those with Other Cancers. Non-Hispanic Black dementia patients with history of other cancers cancer (other than breast, prostate, lung, colorectal, testicular, and cervical) and Non-Hispanic White dementia patients with history of other cancers demonstrate similar cognitive impairment at baseline and progress similarly, but those of Other races demonstrate faster decline. Similar cognitive impairment at baseline and rates of progression are seen for those without cancer history regardless of race. However, those without cancer history demonstrated lower cognition at baseline compared to those with any cancer history.

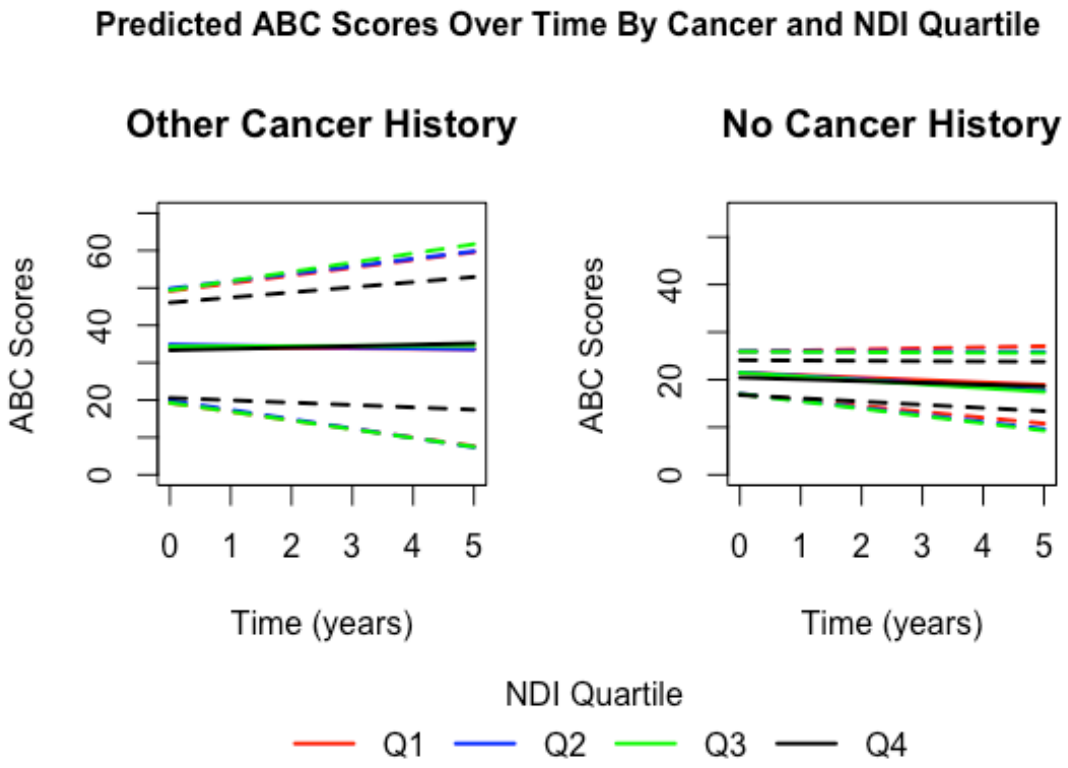

Figure 6. Predicted Alabama Brief Cognitive Screener (ABCs) Scores Over Time by NDI Quartiles in Those with Other Cancer History. Dementia patients have similar baseline cognitive impairment and rate of decline regardless of neighborhood deprivation status. However, those with no cancer history seem to begin with lower cognition at baseline compared to those with other cancer history (other than breast, prostate, lung, colorectal, testicular, and cervical).

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SUPPLEMENTARY MATERIAL

Supplementary Table of Diagnosis Codes / Medications Used for Primary Outcome, Primary Exposure, and Comorbidity Classification			
	ICD-9 Codes	**ICD-10 Codes**	**Medications**
All-Cause Dementia			
Alzheimer's Disease	331.0	G30.9; G30.1; G20.8	
Vascular	290.40; 290.41; 290.42; 290.43; 331.82	F01.50; F01.51	
Dementia with Lewy Bodies	331.82	G31.83	
Frontotemporal	331.1; 331.11; 331.19	G31.0; G31.01; G31.09	
Alcohol Induced	291.2	F10.26; F10.27; F10.97	NA
Other (Creutzfeld-Jakob Disease, Huntington's Disease, Drug-Induced)	046.11; 046.19; 292.82; 333.4	A81.00; A81.01; A81.09; F19.27; F13.27; F13.97; F18.97; F19.17; F19.97; G10	
Not Otherwise Specified	290.0; 290.10; 290.11; 290.12; 290.13; 290.20; 290.21; 290.3; 290.9; 294.1; 294.10; 294.11; 294.20; 294.21; 294.8; 331.2; 787	F03.90; F03.91; F05; F02.80; F02.81; F06.0; F06.8; R41.81; G31.1; R41.9	
Cancer			
Breast	174.0-174.9	C50.011-C50.929; EXCLUDING C50.021-C50.029; C50.121-C50.129; C50.221-C50.229; C50.321-C50.329; C50.421-C50.429; C50.521-C50.529; C50.621-C50.629; C50.821-C50.829; C50.921-C50.929	NA
Colorectal	153.0-153.9; 154.0-154.1	C18.0-C18.9; C19; C20	
Prostate	185	C61	

Lung	162.0-162.9	C33; C34.00-C34.92	
Cervical	180.0-180.9	C53.0-C53.9	
Testicular	186.0-186.9	C62.00-C62.92	
Non-Melanoma Skin	173.00-173.99	C44.00-C44.99	NA
Other	All others from 140.0-208.92	All others from C00.0-C96.Z	
Depression			
	290.13; 290.21; 290.43; 296.2; 296.3; 296.82; 296.9; 296.99; 298; 300.4; 301.1; 305.8; 305.81; 309; 309.1; 311; 969	F32.0; F32.1; F32.2; F32.4; F32.5; F32.9; F33.0; F33.1; F33.2; F33.3; F33.8; F33.9; F34.1; F43.21; F43.23	Amitriptyline; Bupropion; Citalopram; Climipramine; Desipramine; Doxepin; Duloxetine; Escitalopram; Fluoxetine; Fluvoxamine; Imipramine; Maprotiline; Mirtazapine; Nefazodone; Nortriptyline; Paroxetine; Phenelzine; Protriptyline; Sertraline; Selegiline patch; Tranylcypromine; Trimipramine; Venlafaxine ***If on these medications, but with the following codes not considered depressed:** ICD-9: 300.00; 300.01; 300.02; 300.09; 309.81; 338 ICD-10: F41.0; F41.1; F41.3; F41.8; F41.9; F43.10; G89.0-G89.4

Hypertension			
	401.x; 403.0x; 403.1x; 403.9x	I10; I12.0; I12.9; I16.x	Chlorothiazide; Chlorthalidone; Hydrochlorothiazide; Indapamide; Metolazone; HCTZ; Benazepril; Captopril; Enalapril; Fosinopril; Lisinopril; Moexipril; Perindopril; Quinapril; Ramipril; Trandolapril; Azilsartan; Candesartan; Eprosartan; Irbesartan; Losartan; Olmesartan; Telmisartan; Valsartan; Amlodipine; Felodipine; Isradipine; Nicardipine; Nifedipine; Nisoldipine; Diltiazem; Verapamil; Bumetanide; Furosemide; Torsemide; Amiloride; Triamterene; Eplerenone; Spironolactone; Atenolol; Betaxolol; Bisoprolol; Metoprolol; Nebivolol; Nadolol; Propranolol; Acebutolol; Carteolol; Penbutolol; Pindolol; Carvedilol; Labetalol; Aliskiren;

			Doxazosin; Prazosin; Terazosin; Clonidine; Methyldopa; Guanfacine; Hydralazine; Minoxidil
Diabetes			
	250.xx; 357.2; 362.0x; 366.41	E08.36; E08.42; E09.36; E09.42; E10.10; E10.11; E10.29; E10.311; E10.319; E10.36; E10.39; E10.40; E10.42; E10.51; E10.618; E10.620; E10.621; E10.622; E10.628; E10.630; E10.638; E10.641; E10.649; E10.65; E10.69; E10.8; E10.9; E11.00; E11.01; E11.29; E11.311; E11.319; E11.329; E11.339; E11.349; E11.359; E11.36; E11.39; E11.40; E11.42; E11.51; E11.618; E11.620; E11.621; E11.622; E11.628; E11.630; E11.638; E11.641; E11.649; E11.65; E11.69; E11.8; E11.9; E13.10; E13.36; E13.42; E10.37X1; E10.37X2; E10.37X3; E10.37X9; E11.10; E11.11; E11.3291; E11.3292; E11.3293; E11.3299; E11.3391; E11.3392;	Cycloset; Acarbose; Acetohexamide; Albiglutide; Alogliptin; Canagliflozin; Chlorpropamide; Dapagliflozin; Dulaglutide; Empagliflozin; Ertugliflozin; Exenatide; Exenatide ER; Glibenclamide; Glimepiride; Glipizide; Glyburide; Linagliptin; Liraglutide; Lixisenatide; Metformin; Miglitol; Nateglinide; Pioglitazone; Pramlintide; Repaglinide; Rosiglitazone; Saxagliptin; Semaglutide; Sitagliptin; Tolazamide; Tolbutamide; Inhaled insulin; Insulin; Insulin aspart; Insulin degludec; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin human NPH; Insulin

	E11.3393; E11.3399; E11.3491; E11.3492; E11.3493; E11.3499; E11.3591; E11.3592; E11.3593; E11.3599; E11.37X2	human regular; Insulin lispro

ASSOCIATION BETWEEN CANCER TREATMENT AND PROGRESSION OF ALL-CAUSE DEMENTIA

by

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ABSTRACT

Background

Cancer treatments are associated with cancer-related cognitive impairment (CRCI). CRCI and dementia symptoms are similar and could result from the cancer and/or cancer therapies. Limited information exists on the effect of cancer treatments on cognition and its decline in dementia patients.

Methods

Electronic health record data for dementia patients from the University of Alabama at Birmingham were extracted from July 2003 to February 2020. The Alabama Brief Cognitive Screener (ABCs) was used to assess baseline cognition and cognitive progression using linear mixed effects models. Cancer treatments were identified and grouped into categories of: chemotherapy only, hormone therapy only, immunotherapy only, or two or more therapies.

Results

Among dementia patients with cancer history, no statistically significant differences were observed for baseline cognition based on cancer treatment status. However, the absolute difference in mean baseline cognitive score was clinically significantly lower for those on immunotherapies only compared to all other therapy groups (15.2 vs. 18.4 vs. 19.3 vs. 20.1). However, those on immunotherapies only declined both statistically and clinically significantly slower than all other therapy groups (3.4 vs. 0.23 vs. 0.18 vs. -1.52).

Conclusions

In this University-based health system, it was found that immunotherapies result in slower cognitive decline over time relative to those on only chemotherapies, only hormone therapies, and those on two or more therapies. However, sample size was limited. Confirmation of these results in a larger sample is necessary to prompt molecular epidemiological studies and interventions for both CRCI and dementia.

Keywords: Cancer-Related Cognitive Impairment; Cancer Treatments; Dementia Progression; Aging-Related Diseases

INTRODUCTION

Cancer treatments are known to have many immediate side effects such as nausea, vomiting, and fatigue. Additionally, symptoms such as cognitive impairment may arise and persist following treatment. Colloquially this cognitive impairment is known as "chemobrain," and has been well documented as a side effect of not only chemotherapy and other treatment types but also of cancer itself.[1-3] Thus the term "cancer-related cognitive impairment" (CRCI) was coined to reflect this phenomenon.

CRCI results in impairments in the areas of attention, memory, and executive functioning.[1] Between 30-60% of cancer patients experience lasting CRCI following treatment.[1,2] Cognitive reserve, pre-existing cognitive impairment, aging, and cancer treatment have been posited as risk factors for CRCI.[3] A national cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) found that those with a self-reported history of cancer had 40% higher odds of self-reported memory impairment (95% CI: 1.08, 1.83).[4] Another study specifically in colorectal cancer patients from hospitals in Canada and Australia revealed that at each 6-month assessment over the two year follow-up period, approximately 40-50% of patients exhibited cognitive impairment compared to approximately 10-15% of healthy controls.[5]

Recent reviews have summarized evidence relating cancer treatments to cognitive impairment, specifically by the three main cancer treatment types: chemotherapy agents, hormone therapies, and immunotherapies.[1,3] For chemotherapy, it was shown that longer

treatment can result in worse cognitive performance,[6] and that for breast[7] and testicular cancers[8] there is evidence of a potential dose-response relationship where higher doses result in worse cognitive impairment.[1] Specific chemotherapy agents (e.g. methotrexate, 5-fluorouracil, cisplatin, etc.) have been associated with neurological dysfunction,[9-12] and there is evidence, though mixed, that anthracyclines are more neurotoxic than non-anthracycline based chemotherapies.[1,13,14] Hormone therapies used for breast cancer, such as selective estrogen receptor modulators (e.g. tamoxifen) and aromatase inhibitors (e.g. anastrozole), have shown inconsistent results with respect to their effects on cognitive function. A randomized, double-blind, placebo-controlled trial of British women (mean age: 57 years) treated with anastrozole revealed no difference in cognitive impairment compared to placebo.[15] Albeit a weaker study design, a cross-sectional study of anastrozole compared to tamoxifen in US women of comparable age (mean age: 53 years), revealed that those on anastrozole demonstrated worse cognitive performance compared to those on tamoxifen.[16] A Canadian study revealed that women taking either tamoxifen or anastrozole exhibited worse cognition compared to healthy controls.[17] Similarly, androgen-deprivation hormone therapies commonly used in prostate cancer treatment for men have also shown conflicting results.[3] Immunotherapies are attractive clinically because they are designed to target cancer cells specifically rather than being cytotoxic to all cells, but these therapies are relatively new and the evidence for their effect on cognition has not been studied extensively.[3]

We previously showed that patients with a history of cancer have higher baseline cognition at the time of dementia diagnosis, but decline similarly (Aim 1); however, we did not evaluate the role cancer treatments played in this association. To our knowledge,

there are no studies specifically examining the role of cancer treatments on dementia or its progression, thus this study aims to alleviate these gaps by examining the association between cancer treatments and dementia baseline cognition and progression using data from the electronic health record (EHR) from a large, academic medical center in the Southeast.

METHODS

Study Population

This study utilized data from the EHR at the University of Alabama at Birmingham (UAB) obtained from July 2003 to February 2020. UAB is the site of the only National Cancer Institute (NCI)-designated Comprehensive Cancer Center in four states—Alabama, Mississippi, Arkansas, and Louisiana. UAB also is the site of a Memory Disorders Clinic with neurologists and advanced practice nurses trained specifically in the diagnosis, management, and treatment of dementia syndromes. EHR data were obtained using the Informatics for Integrating Biology and the Bedside (i2b2) system.[18] Patients were included in the dataset if meeting the following inclusion criteria: 1) had an International Classification of Diseases (ICD)-9 or ICD-10 diagnosis code of all-cause dementia in any position (see Supplemental Material for specific ICD-9/10 codes), 2) age 50 or older on the date of dementia diagnosis, 3) had two or more cognitive scores as measured on the Alabama Brief Cognitive Screener (ABCs), 4) had an ICD-9/10 diagnosis code of cancer in any position prior to dementia diagnosis, not including central nervous system or only non-melanoma skin cancer (see Supplemental Material for specific ICD-9/10 codes). All Systematized Nomenclature of Medicine (SNOMED) codes throughout the EHR were converted to ICD-10 codes. Participants

were excluded from the dataset if no cancer treatments were present in pharmacy records (regardless of a cancer diagnosis listed in their diagnosis or problems list), but were seen outside of the UAB system for cancer care. A chart review was conducted of participants taking a cancer-related medication without cancer diagnosis codes. Approximately 22 additional cases were identified out of 80 reviewed. This study was approved by the UAB IRB.

Primary Outcome: Alabama Brief Cognitive Screener

The ABCs is a cognitive testing instrument created by Geldmacher et al. for serial cognitive testing in the clinic setting due to copyright of the Mini Mental State Examination (MMSE).[19-21] The ABCs includes measures of several domains of cognitive functioning including orientation, memory, naming, concentration, and repetition. The ABCs has been shown to correlate with the MMSE[22] which has a clinically significant difference of 1-3 points.[23] The ABCs has also demonstrated good internal consistency (Chronbach's alpha=0.85).[19-22,24]

Primary Exposure: Cancer Treatments

We extracted cancer-related medications from pharmacy records on or before the date of dementia diagnosis (see Supplementary Material for list of medications). Each medication was classified according to its drug class (e.g. methotrexate was classified as an anti-metabolite, anastrozole was classified as an anti-estrogen, and bevacizumab was classified as a monoclonal antibody). Classification was completed using Internet search and verified by expert review. Due to sample size in each of these classes, we subsequently collapsed the cancer treatments into the following broad categories:

chemotherapy only, hormone therapy only, immunotherapy only, or two or more therapies. An additional categorical variable within those who were taking two or more therapies was created to examine the effects of specific therapy combinations, including the following categories: chemotherapy + hormone therapy, chemotherapy + immunotherapy, hormone therapy + immunotherapy.

Covariates

Demographics, Health Behaviors, Socioeconomic Status. Demographic information from the date of dementia diagnosis was collected from the EHR including the following: age at diagnosis, sex, race, ethnicity, and marital status. Smoking information was not collected at all visits and was collected as a free-text entry. The smoking status on or closest to the dementia diagnosis date was used and categorized as 'ever' or 'never' smoker as determined from the free text. Race and ethnicity were combined to create a categorical variable including non-Hispanic White, non-Hispanic Black, and other race/ethnicity due to small sample size in other specific races/ethnicities. Marital status was classified as 'married' and other marital statuses were classified as 'other'. Weight and height on or closest to dementia diagnosis, within a maximum of ± 12 months, were used to calculate body mass index (BMI). Extreme values for weight / height were examined and compared to other participant visits. The next closest value was taken for those with impossible values or values inconsistent with other visits.

Socioeconomic status was determined using the Neighborhood Deprivation Index (NDI). ZIP codes obtained at dementia diagnosis were merged with county FIPS codes to construct 9-digit ZIP codes. The NDI methodology has been described elsewhere.[25,26] Briefly, 9-digit ZIP code was merged with United States Census Data regarding

percentage of female-headed households and percentage of households below the poverty line. Specifically, the data were obtained from the American Community Survey 5-year estimates in 2019, which extrapolate back to 2014. The ABCs began use consistently in the Memory Disorders Clinic in 2013 therefore most diagnoses in this dataset were between the years of 2013 and 2019. Percentage of households below the poverty line and percentage of female-headed households were each divided by 10 and the mean of these was taken to calculate the final NDI within the ZIP code. In the previous studies, census tracts were used rather than 9-digit ZIP codes, but EHR data does not possess specific census tract information. In their development of the NDI, Ross and Mirowsky note that ZIP codes are the "next best approximation to a neighborhood" if census tracts are unavailable.[26] Insurance status was collected at dementia diagnosis and categorized as private, government, or other. No participants in this sample had other insurance.

Comorbidities. Depression has been associated with both cancer and dementia. Depression status was determined using a previously described algorithm.[27] Depression diagnoses using ICD-9/10 codes (Supplementary Material) were searched in the diagnosis list and problems list on or before dementia diagnosis, as were medications for depression from the pharmacy list (Supplementary Material) on or before diagnosis of dementia. Participants with either a diagnosis of depression or taking a medication for depression were classified as having depression.

Cardiovascular diseases and risk factors have also been associated with risk for both cancer and dementia. Presence of hypertension and diabetes were determined using multiple criteria. First, the diagnosis and problems lists were searched for ICD-9/10 codes for diabetes and hypertension (specific codes in Supplementary

Material). Secondly, systolic blood pressure, diastolic blood pressure, and glucose levels were obtained by taking the closest value to the dementia diagnosis and within a maximum of 12 months of the diagnosis. Extreme values were compared to other visits and those that were inconsistent or impossible were replaced with the value of the next closest visit. Participants were considered positive for hypertension if systolic blood pressure greater than or equal to 140 mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg. Participants were considered positive for diabetes if glucose level was greater than or equal to 200 mg/dL. Thirdly, pharmacy lists for each participant on or prior to the dementia diagnosis date were searched for hypertensive and diabetic medications (Supplemental Material). An overall hypertension variable and an overall diabetes variable were created whereby participants with hypertension/diabetes diagnosis, hypertension/diabetes medication, and/or elevated blood pressure/glucose values were classified as having the disease. This approach for determining diabetes or hypertension is often used in claims-based data for determination of chronic conditions.[28] Participants missing any predictor were excluded from the model.

Anticholinergic Burden. Several commonly prescribed medications are known to have anticholinergic activity which increases risk of dementia and cognitive impairment.[29,30] Therefore, we calculated anticholinergic burden using a previously defined algorithm.[30] Briefly, all medications on or before the dementia diagnosis were extracted and an anticholinergic burden score assigned for each. The anticholinergic burden scores were summed for each participant to achieve total anticholinergic burden score on dementia diagnosis. A score of ≥3 is considered a clinically relevant anticholinergic burden. The anticholinergic burden score has been shown to predict

cognitive impairment and was compared to other anticholinergic burden scales. This was the most commonly used scale.[31]

Anti-Dementia Medications. Medications to slow cognitive decline in dementia are often prescribed for dementia even before a dementia diagnosis is established.[32] A variable indicating if a participant was taking a dementia-related medication on or after the date of dementia diagnosis was created by searching medication names in the medication data for each participant. Participants were classified as taking a dementia medication if prescribed any of the following: acetylcholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), galantamine (Razadyne); NMDA antagonist memantine (Namenda); and/or memantine + donepezil (Namzaric).

Statistical Analysis

Participant characteristics were described by cancer treatment, using means and standard deviations (SD) for continuous variables and frequency and proportions for categorical variables. Chi-square tests and analysis of variance (ANOVA) for categorical and continuous variables, respectively, were used to assess differences in the characteristics of the sample by cancer treatment. Fisher's exact tests were used where expected cell size was low for categorical variables. Differences in baseline ABCs score (intercept of model) and cognitive decline on the ABCs (slope of model) over time among treatment groups were evaluated using linear mixed effects models (random coefficients models) with a random effect for time.[33] The models were parameterized according to cell means rather than reference-level parameterization. An initial unadjusted model was estimated followed by a final full model adjusting for significant demographic and lifestyle characteristics, comorbidities and medications, including a

priori depression, dementia medications. Age at dementia diagnosis was centered on age 75 for the full model. A propensity score for treatment was created using vascular risk factors as predictors including: smoking, BMI, presence of diabetes, and presence of hypertension. Due to the multinomial nature of the treatment variable, generalized boosted models[34] were used to create the propensity score. To adjust for these vascular risk factors, the full model was then inverse probability of treatment weighted (IPTW) as obtained from the propensity score calculation.[35] for the inverse probability of treatment. Depression and dementia medications were included a priori because depression is associated with both cancer[36] and cognitive decline[37] and dementia medications are known to slow cognitive decline.[38] A basic demographics-adjusted model (age at dementia diagnosis, race, and sex) was also performed within the two or more therapy group specifically examining the exposure of specific therapy combinations.

RESULTS

The sample included 187 participants, of which 74 (39.6%), 75 (40.1%), and 13 (7.0%) had history of taking only chemotherapy, only hormone therapy, and only immunotherapy agents, respectively. Two or more therapies were observed in 26 (13.4%) patients, of which 6 (24.0%) were taking a chemotherapy agent + immunotherapy agent, 16 (64.0%) taking a chemotherapy agent + hormone therapy, and 3 (12.0%) taking hormone therapy + an immunotherapy agent. The mean (SD) age at time of dementia diagnosis was 75.0 (8.4), with no difference in age by cancer treatment status (p=0.2580). There were also no significant differences in other demographic variables assessed. However, a smaller proportion of females used immunotherapy only compared to the other treatment groups (66.7% vs 71.0%, 78.1%, 87.5%) (Table 1). There was also a

lower proportion of non-Hispanic Blacks receiving only hormone therapy compared to the other treatment groups (16.4% vs. 20.3%, 25.0%, 29.2%), and lower proportions of people of other races and ethnicities in the chemotherapy only (2.9%) and two or more therapy group (4.2%) compared to hormone or immunotherapy only groups (each 8.3%) (Table 1).

With respect to health variables, systolic blood pressure (SBP), diabetes, and total anticholinergic burden score differed significantly by treatment status. Mean (SD) systolic blood pressure was lower in the two or more therapy group [124.6 (16.2)] compared to the other treatment groups (136.2 vs. 132.2 vs. 137.1; $p = 0.036$). Participants only on hormone therapy were less likely to have diabetes (26.0%), whereas, participants only on immunotherapy were more likely (66.7%) to have diabetes compared to those only on chemotherapy or two or more therapies (39.1% vs. 37.5%; $p = 0.038$) [Table 1]. Total mean ± SD anticholinergic burden score was highest for those only on immunotherapy treatments (12.7 ± 8.0), and lowest in those only taking hormone therapies (6.5 ± 5.8; $p = 0.009$). All other health characteristics were similar between the two groups.

Mean (SD) unadjusted baseline cognition for the chemotherapy only, hormone therapy only, immunotherapy only, and two or more treatment groups was 19.1 (5.8), 17.6 (5.1), 15.5 (3.5), 17.8 (3.4), respectively. The initial unadjusted model revealed no significant differences in baseline ABCs score or decline over time were found by therapy type (Table 2). The full model adjusted for age centered at 75 years, race, sex, total anticholinergic burden score, depression, dementia medication status, and IPTW weighted for propensity score of treatment based on vascular risk factors. In this model,

baseline ABCs score was significantly lower in those taking immunotherapies relative to all other therapy groups (15.2 vs. Chemotherapy only: 18.4; Hormone therapy only: 19.3; Two or more therapies: 20.1) [Table 2]. With respect to progression, those on immunotherapy demonstrated significantly slower decline per year on the ABCs relative to all other groups (3.4 vs. Chemotherapy only: 0.23; Hormone therapy only: 0.18; Two or more therapies: -1.52) [Table 2].

Deeper examination of those taking two or more therapies was limited based on sample size. In the unadjusted model, no significant differences were revealed in baseline cognition or progression over time for any chemotherapy + immunotherapy, chemotherapy + hormone therapy, or hormone therapy + immunotherapy (Table 3). Those taking hormone therapy + immunotherapy showed a non-significant lower mean cognition at baseline compared to those taking chemotherapy + hormone therapy and those taking chemotherapy + immunotherapy (11.94 vs. Chemo + Immuno: 20.01, Chemo + Hormone: 21.26), but had slower mean decline per year (1.04 vs. Chemo + Immuno: -0.19; Chemo + Hormone: -2.49).

DISCUSSION

In this study evaluating the effects of cancer treatment on cognition and cognitive progression in patients with all-cause dementia from a University-based health system in the Southeast, dementia patients taking immunotherapies had the lowest mean baseline cognitive score, however, declined slower relative to those taking the other treatment types. There were no differences between baseline cognition or decline between dementia patients taking only chemotherapy, only hormone therapy, or those taking two or more therapy types.

Although significant associations were not found with respect to the effect of cancer treatment on baseline cognition and cognitive decline for chemotherapy and hormone therapy, the absolute difference between the mean cognitive scores at baseline is in the clinically significant range with those taking chemotherapy only and hormone therapy only having mean cognitive score ~3 points higher than those taking immunotherapy and ~1 point lower than those taking two or more therapies. However, the absolute difference in mean cognitive decline per year was clinically significantly faster for those taking chemotherapy only, hormone therapy only, and two or more therapies relative to immunotherapy. Thus, the overall trend of these results is consistent with previous studies indicating cognitive impairment in patients taking chemotherapy,[2,3,5-7,39-41] and common hormone therapies for breast cancer[16,17] and prostate cancer[42,43] Despite the inability to conduct a specific analysis by cancer type, hormone therapies are primarily used in breast and prostate cancers and the decline results are consistent with studies indicating that androgen-deprivation therapy for prostate cancer has also been associated with increased risk of dementia, but inconsistent with studies indicating hormone modulating therapies for breast cancer have been associated with reduced risk of neurodegenerative disease.[44-47] However, due to sample size restrictions, we were unable to evaluate androgen-deprivation therapies and estrogen modulating therapies individually. Future analyses should examine these differences.

Very little data exist on the effects of immunotherapy on cognition. The current results show that dementia patients with a history of cancer receiving immunotherapies had lower mean cognition at baseline when examining the absolute difference in mean cognitive score between immunotherapies and all other therapy types and those on two or

more therapies. These results add to the extant literature regarding immunotherapies and their effect on cognition. On the molecular level, the available data indicate that checkpoint inhibitors, one type of immunotherapy typically used concomitant with chemotherapy or radiation, can lead to inflammation, which can subsequently lead to decreased cognition.[48] Chimeric antigen receptor T-cell therapy, another type of immunotherapy, can lead to cytokine storms, which are commonly neurotoxic.[48] Both checkpoint inhibitors and chimeric antigen receptor T-cell therapy can negatively impact multiple organs and systems, including the brain, leading to cognitive impairment via indirect mechanisms.[48] The results of the current study seem to support the evidence from molecular studies that immunotherapies are associated with lower cognition at dementia baseline relative to all other therapies. However, dementia progression seems to be slower, with dementia patients on immunotherapies declining significantly slower than those on all other therapies and those on two or more therapies, which seems counterintuitive given the molecular evidence of neurotoxicity. Further studies comparing those treated with chemotherapies, hormone therapies, and immunotherapies to those who received only surgery or surgery plus radiation will aid in a more definitive determination of cancer therapies' effects on cognition in dementia.

This study has many strengths. First, this is the first study to examine the association between specific cancer treatments and cognition in dementia patients. Secondly, this study was conducted in a population including approximately 20% non-White participants, individuals from a wide array of socioeconomic statuses, and participants with comorbidities including depression, diabetes, and/or hypertension. This

study also evaluated several potential confounders such as comorbidities, anticholinergic burden, and cardiovascular risk to reduce the possibility of residual confounding.

Despite its strengths, this study does have limitations. First, some participants may have received therapies not recorded in the EHR. For example, hormone therapies are typically prescribed long-term so patients may have presented to a non-oncology visit at UAB where hormone therapy was recorded as a current active medication, but receipt of chemotherapy or other short-term cancer therapies were undocumented in the EHR since primary cancer treatment was not completed at UAB. Future studies are planned to examine these treatment associations with more robust measures of treatment. Secondly, some participants may have received cancer treatment after the dementia diagnosis that would affect the rate of cognitive decline, though all patients with cancer in this sample had an initial cancer diagnosis prior to the dementia diagnosis. Future analyses incorporating cancer treatment as a time-varying variable are being explored. Additionally, cancer-staging information is not available. It is possible that those at more severe cancer stages received more aggressive treatments or did not survive long enough to develop dementia. Since all cancer patients in this sample survived long enough to develop dementia it may be appropriate to assume that most cancers were diagnosed in earlier stages. Death information is inconsistent in the EHR, but future studies should examine the competing risk of death. Due to sample size limitations, we were unable to evaluate treatment effects on specific cancer types. This is a goal for future analyses. Dementia medication use was an important confounder in this study, and there could have been misclassification depending on when the medications were started. We evaluated dementia medication use on the date of dementia diagnosis and at any time

thereafter, but if medications were prescribed earlier and discontinued before dementia diagnosis or not recorded and still being used, the participant would be misclassified. If misclassification were present, it is expected to be non-differential between the treatment groups and therefore bias results toward the null. It was also impossible to know the exact dementia syndrome for everyone as diagnoses are not billed according to their specific syndrome, rather often as dementia not otherwise specified (NOS).[49] However, in our previous work in this dataset, we conducted a chart review of dementia, NOS cases to elucidate more information on dementia pathology where about a quarter of participants did not have discernable dementia pathology. Most others were either Alzheimer's disease, vascular dementia, dementia with Lewy bodies, or mixed pathology (Aim 1). Similarly, misclassification in other important confounders was possible. To minimize misclassification, we used a variety of methodologic techniques including the following: 1) used a 12- month look back period to ascertain variables such as BMI, smoking, and comorbidities, as routinely used in administrative claims-based studies,[50,51] 2) classified smoking as 'ever' or 'never', to minimize bias, particularly given it is not expected that older adults would transition from a never smoker to an ever smoker late in life, 3) employed commonly used algorithms to identify the comorbidities of interest, and 4) utilized a 9-digit ZIP code data in the calculation of NDI, which has been indicated to be a reasonable measure of the neighborhood level when census tracts are unavailable. Again, if misclassification occurred in these aforementioned variables, it is not expected to be differential and would therefore bias results toward the null.

CONCLUSIONS

Cancer survival has improved over the past several years due to progress in treatment, prevention, and screening.[52] Given the prevalence of CRCI, many of these older adult cancer survivors will experience persistent CRCI.[1,2] Cancer treatments have been shown to result in cognitive impairment similar to that experienced in patients with dementia syndromes. Previous studies have indicated that dementia patients with history of cancer present with higher cognition at baseline than dementia patients without history of cancer, but overall progress at a similar rate (Aim 1). The current study revealed that cancer treatments, particularly immunotherapies, may affect baseline cognition. However, these current results revealed slower cognitive decline over time for those on specific cancer treatments, again specifically related to immunotherapy compared to those on other therapies and two or more therapies. Sample size limitations induce the need for further study of specific cancer treatments on dementia progression in a more robust sample, but do provide evidence for important late-term effects of cancer treatments on cognition specifically in dementia syndromes. Larger studies should examine these associations in a more robust sample. Consistent results in larger studies may lead to molecular epidemiological studies of cancer treatments with respect to both CRCI and dementia.

Table 1. Participant Characteristics by Treatment Status*

	Chemotherapy Only	Hormone Therapy Only	Immunotherapy Only	Two or More Therapies	p-value
Demographics					
Age at Dementia Diagnosis	73.4 ± 8.5	76.3 ± 8.6	76.3 ± 5.8	75.0 ± 8.1	0.2580
Sex					0.3327
Male	20 (29.0)	16 (21.9)	4 (33.3)	3 (12.5)	
Female	49 (71.0)	57 (78.1)	8 (66.7)	21 (87.5)	
Race					0.4936
Non-Hispanic White	53 (76.8)	54 (74.0)	8 (66.7)	16 (66.7)	
Non-Hispanic Black	14 (20.3)	12 (16.4)	3 (25.0)	7 (29.2)	
Other	2 (2.9)	1 (8.3)	1 (8.3)	1 (4.2)	
Marital Status					0.1337
Married	41 (63.1)	38 (55.9)	9 (75.0)	9 (39.1)	
Other	24 (36.9)	30 (44.1)	3 (25.0)	14 (60.9)	
NDI†	0.8 ± 0.6	0.8 ± 0.6	1.1 ± 0.7	0.7 ±0.6	0.8729
Insurance Status					0.2704
Private	8 (11.9)	7 (9.6)	0 (0.0)	0 (0.0)	
Government	59 (88.1)	66 (90.4)	12 (100.0)	23 (100.0)	
Health Variables					
Smoking					0.2583
Ever	39 (56.5)	44 (60.3)	6 (50.0)	12 (52.2)	
Never	30 (43.5)	29 (39.7)	6 (50.0)	11 (47.8)	
BMI (kg/m^2)	26.7 ± 4.9	26.2 ± 5.1	27.8 ± 8.0	26.3 ± 5.6	0.9447
SBP (mmHg)†	136.2 ± 21.0	132.2 ± 20.3	137.1 ± 26.6	124.6 ± 16.2	**0.0364**
DBP (mmHg)†	73.7 ± 10.3	72.8 ± 10.3	72.3 ± 11.4	73.7 ± 7.2	0.8736
Glucose Level (mg/dL)	128.6 ± 60.8	116.5 ± 32.7	111.7 ± 39.8	118.6 ± 39.3	0.3377
Depression†					0.8032
Yes	45 (80.4)	49 (76.6)	10 (90.9)	17 (81.0)	
No	11 (19.6)	15 (23.4)	1 (9.1)	4 (19.0)	

Dementia Medication[†]					0.6851
Yes	40 (58.0)	41 (56.2)	5 (41.7)	15 (62.5)	
No	29 (42.0)	32 (43.8)	7 (58.3)	9 (37.5)	
Hypertension[†]					0.7964
Yes	61 (88.4)	66 (90.4)	11 (91.7)	20 (83.3)	
No	8 (11.6)	7 (9.6)	1 (8.3)	4 (16.7)	
Diabetes[†]					**0.0384**
Yes	27 (39.1)	19 (26.0)	8 (66.7)	9 (37.5)	
No	42 (60.9)	54 (74.0)	4 (33.3)	15 (62.5)	
Total Anticholinergic Burden[†]	7.9 ± 7.3	6.5 ± 5.8	12.7 ± 8.0	11.6 ± 6.4	**0.0086**
Cancer Type					**0.0005**
Breast	1 (2.9)	15 (22.7)	0 (0.0)	2 (8.3)	
Colorectal	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	
Non-Melanoma Skin	2 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	
Prostate	3 (8.8)	9 (13.6)	0 (0.0)	0 (0.0)	
Other	21 (61.8)	2 (3.0)	7 (77.8)	6 (25.0)	
Two or More	6 (17.6)	40 (66.6)	2 (22.2)	16 (66.7)	

[*]Evaluated using ANOVA and chi-square tests / Fisher's exact tests (where necessary) for continuous and categorical variables, respectively. Significance set at $\alpha=0.05$

[†]NDI: neighborhood deprivation index based on algorithm published by Ross et al.; BMI: body mass index calculated using height / weight closest to dementia diagnosis within 1 year of diagnosis; SBP: systolic blood pressure, on or closest to dementia diagnosis within 1 year of diagnosis; DBP: diastolic blood pressure, on or closest to dementia diagnosis within 1 year of diagnosis; glucose level: on or closest to dementia diagnosis within 1 year of diagnosis; depression: based on algorithm published by Trinh et al.; dementia medication: donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), memantine (Namenda), and/or donepezil + memantine (Namzaric); hypertension: based on SBP $\geq$ 140 mmHg / DBP $\geq$ 90 mmHg, diagnosis of hypertension prior to dementia diagnosis, and/or presence of hypertensive medications prior to dementia diagnosis; diabetes: based on glucose of $\geq$ 200 mg/dL, diagnosis of diabetes prior to dementia diagnosis, and/or presence of diabetic medications prior to dementia diagnosis; total anticholinergic burden: prior to dementia diagnosis based on algorithm published by Boustani et al.

Table 2. Estimates of Mean Cognitive Performance at Baseline and Decline Over Time by Cancer Treatment Status*

	Model 1†	**Model 2‡**
	β (95% CI)	**β (95% CI)**
Chemotherapy Only		
Intercept	21.10 (19.61, 22.59)	18.40 (15.84, 20.96)
Slope	-0.43 (-1.38, 0.53)	0.23 (-0.97, 1.43)
Hormone Therapy Only		
Intercept	21.05 (19.44, 22.67)	19.29 (16.79, 21.79)
Slope	0.26 (-0.72, 1.24)	0.18 (-1.01, 1.37)
Immunotherapy Only		
Intercept	19.82 (16.26, 23.44)	**15.20 (10.98, 19.42)**
Slope	2.11 (-0.53, 4.75)	**3.35 (0.98, 5.73)**
Two or More Therapies		
Intercept	20.74 (18.04, 23.44)	20.06 (16.48, 23.64)
Slope	-0.54 (-2.09, 1.00)	-1.52 (-3.27, 0.23)

*Estimated using linear mixed effects models with a random effect for time. Parameterized using cell means. Cognition measured using the Alabama Brief Cognitive Screener (ABCs). Significance set at α=0.05. Intercept indicates the mean ABCs score at dementia baseline according to treatment, slope indicates the mean decline per year on the ABCs according to treatment.

†Unadjusted

‡Adjusted for age at dementia diagnosis centered on age 75 years, race, sex, total anticholinergic burden before dementia diagnosis, depression status on or before dementia diagnosis, taking a dementia medication on or before dementia diagnosis, and inverse probability of treatment weighted for vascular risk factors (smoking, body mass index, hypertension status, and diabetes status)

Table 3. Estimates of Mean Cognitive Performance at Baseline and Decline Over Time Based on Cancer Therapy Combinations*

	Model 1†	**Model 2‡**
	β (95% CI)	**β (95% CI)**
Chemotherapy + Immunotherapy		
Intercept	20.87 (14.82, 26.91)	20.01 (5.60, 34.42)
Slope	0.25 (-6.44, 6.94)	-0.19 (-6.54, 6.15)
Chemotherapy + Hormone Therapy		
Intercept	18.88 (15.81, 21.95)	21.26 (7.21, 35.30)
Slope	0.41 (-1.22, 2.04)	-2.49 (-5.83, 0.85)
Immunotherapy + Hormone Therapy		
Intercept	23.34 (17.11, 29.58)	11.94 (-11.65, 35.53)
Slope	-1.34 (-3.86, 1.17)	1.04 (-4.91, 6.98)

*Estimated using linear mixed effects models with a random effect for time. Parameterized using cell means. Cognition measured using the Alabama Brief Cognitive Screener. Significance set at α=0.05. Intercept indicates the mean ABCs score at dementia baseline according to treatment combination, slope indicates the mean decline per year on the ABCs according to treatment combination.

†Unadjusted

‡Adjusted for age at dementia diagnosis centered on age 75 years, race, sex, total anticholinergic burden before dementia diagnosis, depression status on or before dementia diagnosis, taking a dementia medication on or before dementia diagnosis, and inverse probability of treatment weighted for vascular risk factors (smoking, body mass index, hypertension status, and diabetes status)

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SUPPLEMENTARY MATERIAL

Supplementary Table of Diagnosis Codes / Medications Used for Primary Outcome, Primary Exposure, and Comorbidity Classification			
	ICD-9 Codes	**ICD-10 Codes**	**Medications**
All-Cause Dementia			
Alzheimer's Disease	331.0	G30.9; G30.1; G20.8	
Vascular	290.40; 290.41; 290.42; 290.43; 331.82	F01.50; F01.51	
Dementia with Lewy Bodies	331.82	G31.83	
Frontotemporal	331.1; 331.11; 331.19	G31.0; G31.01; G31.09	
Alcohol Induced	291.2	F10.26; F10.27; F10.97	NA
Other (Creutzfeld-Jakob Disease, Huntington's Disease, Drug-Induced)	046.11; 046.19; 292.82; 333.4	A81.00; A81.01; A81.09; F19.27; F13.27; F13.97; F18.97; F19.17; F19.97; G10	
Not Otherwise Specified	290.0; 290.10; 290.11; 290.12; 290.13; 290.20; 290.21; 290.3; 290.9; 294.1; 294.10; 294.11; 294.20; 294.21; 294.8; 331.2; 787	F03.90; F03.91; F05; F02.80; F02.81; F06.0; F06.8; R41.81; G31.1; R41.9	
Cancer			
Breast	174.0-174.9	C50.011-C50.929; EXCLUDING C50.021-C50.029; C50.121-C50.129; C50.221-C50.229; C50.321-C50.329; C50.421-C50.429; C50.521-C50.529; C50.621-C50.629; C50.821-C50.829; C50.921-C50.929	**Chemotherapy**: ***Alkylating Agents:*** Carboplatin, Busulfan, Cyclophosphamide, Dacarbazine, Melphalan, Oxaliplatin, Temozolomide ***Anthracycline***: Doxorubicin
Colorectal	153.0-153.9; 154.0-154.1	C18.0-C18.9; C19; C20	***Anti-Metabolites:***

Prostate	185	C61	Capecitabine,
Lung	162.0-162.9	C33; C34.00-C34.92	Cytarabine, Fludarabine,
Cervical	180.0-180.9	C53.0-C53.9	Gemcitabine,
Testicular	186.0-186.9	C62.00-C62.92	Hydroxyurea,
Non-Melanoma Skin	173.00-173.99	C44.00-C44.99	Methotrexate; ***Anti-Tumor Antibiotic:*** Bleomycin, Mitomycin; ***Kinase Inhibitors:*** Bosutinib, Erlotinib, Everolimus, Ibrutinib, Imatinib, Nilotinib, Nintedanib, Osimertinib, Palbociclib; ***Podophyllotoxin Derivative:*** Etoposide; ***Proteasome Inhibitors:*** Bortezomib, Ixazomib; ***Purine Antagonist:*** Mercaptopurine; ***Taxanes:*** Docetaxel, Paclitaxel; ***Vinca Alkyloids:*** Vincristine
Other	All others from 140.0-208.92	All others from C00.0-C96.Z	**<u>Hormone Therapy</u>** ***Anti-Androgens:*** Abiraterone, Bicalutamide, Flutamide ***Anti-Estrogens:*** Anastrozole, Bazedoxifene-Conjugated Estrogens, Exemestane, Fulvestrant,

			Letrozole, Tamoxifen; ***GNRH Agonists:*** Leuprolide, Triptorelin; **<u>Immunotherapy:</u>** Anti-Angiogenic: Bevacizumab; ***Antibody Drug Conjugate:*** Brentuximab Vedotin; ***Biologic Response Modifier:*** BCG; ***Immunomodulators:*** Lenalidomide, Lymphocyte Immune Globulin (anti-thy (equine)), Thalidomide; ***Monoclonal Antibodies:*** Daratumumab, Elotuzumab, Pembrolizumab, Rituximab, Trastuzumab
Depression			
	290.13; 290.21; 290.43; 296.2; 296.3; 296.82; 296.9; 296.99; 298; 300.4; 301.1; 305.8; 305.81; 309; 309.1; 311; 969	F32.0; F32.1; F32.2; F32.4; F32.5; F32.9; F33.0; F33.1; F33.2; F33.3; F33.8; F33.9; F34.1; F43.21; F43.23	Amitriptyline; Bupropion; Citalopram; Climipramine; Desipramine; Doxepin; Duloxetine; Escitalopram; Fluoxetine; Fluvoxamine; Imipramine; Maprotiline; Mirtazapine; Nefazodone; Nortriptyline; Paroxetine;

			Phenelzine; Protriptyline; Sertraline; Selegiline patch; Tranylcypromine; Trimipramine; Venlafaxine ***If on these medications, but with the following codes not considered depressed:** ICD-9: 300.00; 300.01; 300.02; 300.09; 309.81; 338 ICD-10: F41.0; F41.1; F41.3; F41.8; F41.9; F43.10; G89.0-G89.4
Hypertension			
	401.x; 403.0x; 403.1x; 403.9x	I10; I12.0; I12.9; I16.x	Chlorothiazide; Chlorthalidone; Hydrochlorothiazide; Indapamide; Metolazone; HCTZ; Benazepril; Captopril; Enalapril; Fosinopril; Lisinopril; Moexipril; Perindopril; Quinapril; Ramipril; Trandolapril; Azilsartan; Candesartan; Eprosartan; Irbesartan; Losartan; Olmesartan; Telmisartan; Valsartan; Amlodipine; Felodipine; Isradipine; Nicardipine; Nifedipine;

			Nisoldipine; Diltiazem; Verapamil; Bumetanide; Furosemide; Torsemide; Amiloride; Triamterene; Eplerenone; Spironolactone; Atenolol; Betaxolol; Bisoprolol; Metoprolol; Nebivolol; Nadolol; Propranolol; Acebutolol; Carteolol; Penbutolol; Pindolol; Carvedilol; Labetalol; Aliskiren; Doxazosin; Prazosin; Terazosin; Clonidine; Methyldopa; Guanfacine; Hydralazine; Minoxidil
Diabetes			
	250.xx; 357.2; 362.0x; 366.41	E08.36; E08.42; E09.36; E09.42; E10.10; E10.11; E10.29; E10.311; E10.319; E10.36; E10.39; E10.40; E10.42; E10.51; E10.618; E10.620; E10.621; E10.622; E10.628; E10.630; E10.638; E10.641; E10.649; E10.65; E10.69; E10.8; E10.9; E11.00; E11.01; E11.29; E11.311; E11.319; E11.329; E11.339; E11.349; E11.359;	Cycloset; Acarbose; Acetohexamide; Albiglutide; Alogliptin; Canagliflozin; Chlorpropamide; Dapagliflozin; Dulaglutide; Empagliflozin; Ertugliflozin; Exenatide; Exenatide ER; Glibenclamide; Glimepiride; Glipizide; Glyburide; Linagliptin; Liraglutide; Lixisenatide;

	E11.36; E11.39; E11.40; E11.42; E11.51; E11.618; E11.620; E11.621; E11.622; E11.628; E11.630; E11.638; E11.641; E11.649; E11.65; E11.69; E11.8; E11.9; E13.10; E13.36; E13.42; E10.37X1; E10.37X2; E10.37X3; E10.37X9; E11.10; E11.11; E11.3291; E11.3292; E11.3293; E11.3299; E11.3391; E11.3392; E11.3393; E11.3399; E11.3491; E11.3492; E11.3493; E11.3499; E11.3591; E11.3592; E11.3593; E11.3599; E11.37X2	Metformin; Miglitol; Nateglinide; Pioglitazone; Pramlintide; Repaglinide; Rosiglitazone; Saxagliptin; Semaglutide; Sitagliptin; Tolazamide; Tolbutamide; Inhaled insulin; Insulin; Insulin aspart; Insulin degludec; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin human NPH; Insulin human regular; Insulin lispro

CANCER HISTORY IS RELATED TO NEUROLOGIC SPECIALTY CARE IN PATIENTS WITH DEMENTIA

by

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ABSTRACT

Background

Incidence and prevalence of aging-related diseases like dementia and cancer are increasing along with cancer survival rates. Cancer and its treatments are associated with cognitive effects resembling dementia. Guidelines advise cancer patients return to primary care follow-up after remission and be referred to specialists for cognitive complications. It is unclear if these guidelines are followed.

Methods

Electronic health record data at the University of Alabama at Birmingham were extracted from July 2003 to May 2020. Specialty care utilization on and after dementia diagnosis was compared by cancer history status. Factors associated with specialty care utilization were examined using logistic regression.

Results

This study included 17,078 patients with dementia, of which 2,534 (14.8%) had cancer history. Those with cancer history were older (77.0 vs. 75.4 years) and more likely to be non-Hispanic White/Black (93.0% vs. 88.7%). Specialty care utilization was lower for those with versus without cancer history on (11.3% vs. 17.1%; p: <0.0001) and after dementia diagnosis (13.5% vs. 19.2%; p: <0.0001). Age at diagnosis (OR: 0.97 [0.97 - 0.98]), anticholinergic burden (OR: 0.95 [0.94 – 0.96]), socioeconomic status (OR: 0.89 [0.80 – 0.98]), and vascular factors (OR: 0.01 [0.00 – 0.03]) were associated with lower odds of specialty care on or after dementia diagnosis.

Conclusions

In this University-based medical system, cancer survivors with dementia were less likely to utilize specialty care than those without. Several factors predicted specialty care utilization. Studies should assess barriers to primary care referral to specialty care for cancer survivors with cognitive impairment.

Keywords: specialty care utilization; dementia; cancer; cognitive impairment

INTRODUCTION

The United States (US) continues to undergo an epidemiological shift in its demographics, where the average age of the population grows older.[1] As this occurs, rates for cancer, one of the most prevalent aging-related conditions, are expected to continue to increase.[2] Due to advancements in cancer screening, treatment, and prevention, the survival rate for many of the most common cancers has increased,[3,4] thus, the number of long-term cancer survivors has increased.

Cancer survivorship, the period from diagnosis throughout the remainder of life, is a growing field of research.[4] There are many aspects to consider including late and long-term effects of cancer and its treatments. Premature aging is a well-documented phenomenon in cancer survivorship, with increased rates of cardiovascular dysfunction, osteoporosis, sarcopenia, and more.[4-8] Moreover, cognitive impairment is a known side effect of cancer itself, and from the therapies used during the treatment process. This cognitive impairment can persist long after treatment completion.[9-11]

This cognitive impairment, referred to as cancer-related cognitive impairment (CRCI), results in impairment in attention, memory, and executive functioning,[9-11] and mimics the impairments seen in dementia patients.[12] Similar cognitive consequences should logically pre-dispose those with CRCI to develop dementia as they age, especially since risk for dementia increases with age.[12] However, many cross-sectional studies have noted decreased risk of Alzheimer's disease and related dementias (ADRD) after cancer and vice versa, cross-sectionally.[13-16] Longitudinal studies, including those by our group,

have demonstrated that for those who do develop ADRD following cancer, their cognition at ADRD diagnosis is better than those who develop ADRD without a preceding cancer diagnosis (Aim 1).[17] Cancer history, however, has shown no effect on progression of dementia or cognitive decline. An observational study of 1,271 mostly White, healthy participants with mild cognitive impairment (MCI) and Alzheimer's disease (AD) indicated no difference in cognitive progression over time between those with and without cancer history and who have prevalent AD.[17] Similarly, our study utilizing clinical data in all-cause dementia patients from a University-based health system in the Southeast US, revealed no difference in progression over time among those with history of cancer compared to those without cancer history (Aim 1). Cancer treatments have been posited to play a role in the presence of CRCI, but evidence is mixed and limited.[9,11] Our group preliminarily examined the relationship between cancer treatments and cognitive progression in dementia patients with cancer history and revealed lower baseline cognitive score, but slower cognitive decline over time for those taking only immunotherapy compared to those taking only chemotherapy, only hormone therapy, or those taking two or more cancer therapies (Aim 2).

Although there are neuro- and pathophysiological mechanisms that associate cancer and the medications used to treat it with poor cognition, it is possible that other factors are playing a role in explaining the associations between cancer and cognitive decline. Access to care plays a role in outcomes of almost all health conditions, and for dementia, earlier diagnoses leads to slower disease progression.[18] Per guidelines from the American Cancer Society, [19-22] primary care physicians of breast cancer survivors should inquire as to the patient's cognitive status, evaluate and treat reversible causes of these

deficits, and refer to specialty care for further assessment and treatment if needed.[19] Guidelines for other common cancers including prostate, colorectal, and head / neck cancers are less detailed, but do outline the need for frequent history and physical and close monitoring for long-term and late effects of cancer and its treatments particularly in the first year after treatment completion.[20-22]

Unfortunately, it is unclear if these guidelines are being followed. Considering primary care follow-up of cancer patients, there could be missed and/or delayed diagnoses of dementia as is common in primary care.[23] Reasons for this are many and may be related to provider factors such as that they often do not receive training in dementia diagnostics, lack time to evaluate for cognitive impairment in the clinic, and may not refer for specialty care due to access to care issues among their patients.[23,24] Patient or caregiver factors may also contribute whereby patients or caregivers assume that the cognitive decline being observed is related to normal aging or side effects of other comorbidities or medications, and may not follow through with specialty care.[23]

Given the importance of specialty neurologic care for dementia, the goal of this study is to evaluate the proportion of specialty care service use in all-cause dementia patients both with and without cancer history and to examine predictors of specialty care utilization.

METHODS

Study Population

The data for this study were obtained from the EHR at the University of Alabama at Birmingham (UAB) from July 2003 to May 2020. UAB houses the only National

Cancer Institute (NCI)-designated Comprehensive Cancer Center in Alabama, Mississippi, Arkansas, and Louisiana. UAB also has a Memory Disorders Clinic with physicians and advanced practice nurses trained in diagnostics and management of ADRD. The Informatics for Integrating Biology and the Bedside (i2b2) system.[25] Patients were included if they: 1) had an International Classification of Diseases (ICD)-9 or ICD-10 diagnosis code in any position of ADRD on the problems list and/or diagnosis list (see Supplemental Material for specific ICD-9/10) and 2) were age 50 or older on dementia diagnosis. Cancer exposure required an ICD-9/10 diagnosis code in any position from the problems list, diagnosis list, and/or the UAB tumor registry. of cancer not including central nervous system (CNS) before diagnosis of dementia (see Supplemental Material for specific ICD-9/10 codes). The UAB tumor registry is a registry in the EHR of patients diagnosed and treated for cancer at UAB. Systematized Nomenclature of Medicine (SNOMED) codes were converted to ICD-10 codes. Encounters were excluded if no visit location or service was specified. This study was approved by the UAB IRB.

Primary Outcome: Visit in Specialty Care on Dementia Diagnosis

The primary outcome for this study was a dementia related specialty care visit on the date of dementia diagnosis. Dementia-related specialty care was defined as geriatrics, neurology, neurosurgery, psychiatry, or geriatric psychiatry.[26] All other visit locations were considered as "not dementia-related specialty care." The EHR data are structured by encounter where each encounter is a separate presentation to the health system, either outpatient or inpatient. Other encounters not classified as specialty visits, included those where the dementia diagnosis came from hospital units, or those where the dementia

diagnosis was only located in the problem lists in specialty clinics, likely due to being diagnosed outside the UAB system.

Secondary Outcomes

Secondary outcomes compared the proportion of patients with 1) specialty care visit compared with no specialty visit any time after the dementia diagnosis, 2) specialty care visit compared with primary care on dementia diagnosis, 3) specialty care compared with primary care visit at any time after the dementia. Primary care was defined as a visit in internal medicine or family practice.[27,28]

Primary Exposure: Cancer Diagnosis History

Cancer diagnosis prior to the dementia diagnosis was the primary exposure for this study. Cancer diagnosis was classified by using ICD-9/10 diagnosis codes as described in the Supplemental Material. ICD-9 and ICD-10 codes were searched in the problem list, diagnosis list, and the tumor registry. The UAB tumor registry is a registry within the EHR of all cancers diagnosed at UAB. CNS cancers were excluded due to adverse cognitive consequences related to CNS tumors and the inability to distinguish dementia from these adverse effects. A category of all cancers was created excluding non-melanoma skin cancer. Specific cancer variables were further created including breast, prostate, colorectal, non-melanoma skin cancer, testicular, cervical, lung, and all other cancers. Another variable was defined for those with two or more cancers.

Covariates

Demographics, Health Behaviors, and Socioeconomic Factors. Demographics were collected at the dementia diagnosis visit including: age at diagnosis, race, ethnicity,

sex, and marital status. Race and ethnicity were combined to create a three-level variable with categories including non-Hispanic White, non-Hispanic Black, and other races/ethnicities. Smoking was collected as a free-text variable, but not collected at every visit. Therefore, the smoking entry on or closest to the dementia diagnosis was used and categorized as 'ever' or 'never' smoker based on the free-text response. For each participant, body mass index (BMI) values in kilograms per meters-squared (kg/m^2) on or closest and within 12 months of the dementia diagnosis were collected. Outliers were identified and values that were not plausible were excluded. Socioeconomic status was defined by using the Neighborhood Deprivation Index (NDI). ZIP codes on dementia diagnosis were combined with county FIPS codes to create 9-digit ZIP codes. Ross et al.[29] has previously defined methodology for creating this index where 9-digit ZIP code was merged with data from the American Community Survey 5-year estimates from 2019, which extrapolate back to 2015. Specifically, the American Community Survey estimates for percentage of female-headed households and percentage of households below the poverty line were used. These percentages were each divided by 10 and the mean of the two were calculated to create NDI for the 9-digit ZIP code. The previous methodology utilized census tracts, but these are not collected in the EHR. However, another paper by Ross and Mirowsky indicates that ZIP codes are the next best neighborhood approximation if census tracts are unavailable.[30] A one-unit increase in NDI corresponded to a 10% increase in the percent of female-headed households and houses below the poverty line. Finally, insurance status on dementia diagnosis was categorized as private, government, or other insurance.

Comorbidities. Depression diagnoses using ICD-9/10 codes were searched in the diagnosis and/or problems list for each participant on or at any time before the dementia diagnosis (specific ICD-9/10 codes listed in Supplementary Material). Depression medications were also searched in the medication list for each participant on or at any time before dementia diagnosis. Participants were classified as having depression if either a code for depression or a prescribed medication for depression was present. Those with neither a depression diagnosis nor medications were classified as not having depression.[31]

To adjust for vascular risk factors smoking, BMI, diabetes, and hypertension we used propensity score methodology. Propensity scores for adjustment of cardiovascular risk was used in many other studies with methodology extensively described elsewhere.[32-34] We used logistic regression to extract the probability of having cancer using the all-cancer group with the vascular risk factors as predictors. Hypertension was classified by using a three-pronged approach. First, ICD-9/10 codes in the diagnosis list and problems list for each participant on or at any time before dementia diagnosis were searched. Secondly, the medication list on or at any time before dementia diagnosis was searched for hypertensive medications. Finally, systolic and diastolic blood pressure levels ± 12 months were collected on or closest to the dementia diagnosis. Extreme values were evaluated and impossible values were set to missing. Participants were considered positive for hypertension if systolic blood pressure was ≥ 140 mmHg and/or diastolic blood pressure was ≥ 90 mmHg. Participants with a hypertension code, medication, and/or systolic / diastolic blood pressure value below the threshold were classified as having hypertension. Participants negative for all three were classified as not having hypertension. Diabetes was classified using a similar three-pronged approach with

codes, medications, and glucose level. Non-fasting glucose level ≥ 200 mg/dL or fasting glucose level ≥ 126 mg/dL were the threshold for biomarker-based diabetes determination. This three-tiered approach is used often in claims-based data for classification of chronic conditions.[35] Specific diagnostic codes and medications are listed in the Supplemental Material.

Anticholinergic Burden. Anticholinergic burden score was assigned to anti-cholinergic medications and the score for each participant was totaled to obtain overall anti-cholinergic burden score at dementia diagnosis.[36] Medications on or at any time before dementia diagnosis were used for this calculation. Anticholinergic activity has been associated with cognitive impairment and risk for dementia.[36,37] A clinically significant anticholinergic burden score is ≥ 3. The anticholinergic burden scale has been shown to predict cognitive impairment and has been compared to other anti-cholinergic burden scales.[38] The anticholinergic burden scale is the most widely used in the literature and has been shown to predict several outcomes.[38]

Medications for Dementia. Many medications are approved to slow dementia-related cognitive decline. A variable for dementia medication use was created. Participants were classified as taking a dementia medication if taking any of the following medications on or at any time after the dementia diagnosis: donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), memantine (Namenda), and/or donepezil + memantine (Namzaric). Some may have initiated these medications prior to dementia diagnosis, but are typically maintained throughout mild to moderate dementia stages.

Statistical Analysis

Characteristics of the sample were described by cancer status, using means and standard deviations (SD) for continuous variables and frequencies and proportions for categorical variables. Differences in participant characteristics between those with any cancer and without a history of cancer were examined with t-tests and chi-square tests for continuous and categorical variables, respectively. Fisher's exact tests were used if expected sample size was less than five for categorical variables. The proportion of participant with visits to specialty care on dementia diagnosis was evaluated by cancer history status (any cancer) using chi-square tests. Chi-square tests were also used to determine the differences in the frequency of the secondary outcomes by cancer history status. Multivariable logistic regression models were used to estimate the odds of patients with cancer history having a specialty visit, as well as to identify factors associated with specialty care utilization. Predictors assessed included all variables significantly different between the two cancer groups. Separate models were fit for each secondary outcome. We evaluated if race or NDI modified the association between cancer history and specialty visit using interaction terms. A sensitivity analysis by cancer type was performed in cancers with a large enough sample size. Statistical significance was assessed at $\alpha=0.05$ and all analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and RStudio 1.2.5033.

RESULTS

Our study included 17,078 patients with dementia of which 2,534 (14.8%) had a history of cancer. Of those with a history of cancer, 273 (10.8%) only had breast cancer, 138 (5.4%) only had colorectal cancer, 113 (4.5%) only had lung cancer, 241 (9.5%) only

had prostate cancer, 34 (1.3%) only had cervical cancer, and 4 (0.2%) only had testicular cancer. Other cancer types were found in 1341 (52.9%) of the sample, and 390 (15.4%) had two or more cancers (Figure 1). Overall, the mean (SD) age at time of dementia diagnosis was 75.6 (11.0); however, those with cancer history were significantly older at dementia diagnosis (77.0 vs. 75.4 years, p: <0.0001), were more likely to be male (45.7% vs. 41.3%, p: <0.0001), Non-Hispanic White (66.5% vs. 62.9%, p: <0.0001), married (47.7% vs. 44.1%, p: 0.0007), and have government insurance (92.5% vs. 87.4%, p: <0.0001) compared to those without cancer history. With respect to health-related variables, those with a history of cancer were significantly more likely to be ever smokers (51.1% vs. 43.9%, p: <0.0001), have depression (66.3% vs. 57.6%, p: <0.0001), hypertension (67.6% vs. 58.4%, p: <0.0001), diabetes (19.1% vs. 13.6%, p: <0.0001), a higher mean vascular propensity score (0.17 vs. 0.16, p: <0.0001), and have a higher total mean anticholinergic burden score (7.7 vs. 5.2, p: <0.0001) compared to dementia patients without a history of cancer [Table 1].

A total of 6,274 (40.3%) patients had specialty care visits on the date of their dementia diagnosis. Those with cancer history were less likely to have their dementia diagnosis from a specialty neurology, psychiatry, or geriatrics clinic than those without cancer history (11.3% vs. 17.1%; p <0.0001). A total of 7,442 (61.9%) patients had specialty care visits any time after dementia diagnosis. After diagnosis of dementia, patients with a history of cancer remained less likely to have visits in specialty clinics compared to those with no prior cancer (13.5% vs. 19.2%; p <0.0001) [Table 2]. Conversely, when considering if the dementia diagnosis was from a specialty compared with primary care visit, those dementia patients with cancer history remained less likely

to have a specialty visit on dementia diagnosis (11.3% vs. 18.5%; p <0.0001). This pattern held for visits any time after the dementia diagnosis (13.5% vs. 21.8%; p <0.0001) [Table 2].

Evaluating Factors Associated with Specialty Visits among Dementia Patients

For the primary outcome of specialty visits on dementia diagnosis, factors associated with lower odds included: age, race/ethnicity, anticholinergic burden, NDI, and vascular propensity score (Table 3). Every one-year increase in age on or after dementia diagnosis was associated with a 3% (OR: 0.97; 95% CI: 0.97 - 0.98) lower odds of specialty visits Compared to Non-Hispanic White patients, Non-Hispanic Black patients had 39% lower odds (OR: 0.61; 95% CI: 0.53 – 0.70) of specialty care visits on dementia diagnosis. A one-unit increase in total anticholinergic burden was associated with 5% lower odds of specialty visit on dementia diagnosis. A one-unit increase in NDI was associated with 11% lower odds of a specialty visit on dementia diagnosis. A one-unit increase in the propensity score was associated with 99% lower odds of a specialty visit on dementia diagnosis. Dementia medications and insurance status were the only two variables associated with higher odds of specialty visits on dementia diagnosis, with being on a dementia medication being associated with 92% (OR: 1.92; 95% CI: 1.74 – 2.12) higher odds of specialty visit, and having private insurance was associated with 2.4-fold higher odds of specialty visit on dementia diagnosis.

Age, anticholinergic burden, NDI, vascular propensity score were also associated with lower odds of specialty visits any time after dementia diagnosis; likewise, dementia medications and insurance were also associated with a higher odds of specialty visits any time after dementia diagnosis (Table 3). Any cancer was only associated with lower odds

of specialty visit use after dementia diagnosis, with cancer history having 15% lower odds (OR: 0.85, 95% CI: 0.74 – 0.98) of specialty visits compared to those with no history of cancer any time after dementia diagnosis. Depression was also only associated with specialty visit use in the after dementia diagnosis outcome, with depression being associated with 21% higher odds of specialty visit use (OR: 1.21, 95% CI: 1.07 – 1.37) (Table 3).

Evaluating Factors Associated with Specialty Visits vs. Primary Care Visits Only among Dementia Patients

Similar to the previous outcomes, age, race, and vascular propensity score were associated with lower odds of specialty visits on or after dementia diagnosis compared to primary care, with similar magnitudes of effect. Any cancer, total anticholinergic burden, and dementia medications had a similar effect size to that observed in the primary outcome, but significant associations were only found when evaluating specialty visits after dementia diagnosis. Dementia medication was the only factors associated with higher odds of specialty visits after dementia diagnosis when comparing to primary care visits.

Does Race or NDI Modify the Association between Cancer History and Special Visits?

A significant race by cancer interaction was detected only for specialty care vs. no specialty care on dementia diagnosis (p-value: 0.0007). On dementia diagnosis, Non-Hispanic Whites with any cancer history had non-significant 3% lower odds of specialty care vs. no specialty care compared to non-Hispanic Whites without cancer history (OR: 0.97, 95% CI: 0.83 – 1.14), Non-Hispanic Blacks with any cancer history had 9% higher

odds of specialty care vs. no specialty care compared to non-Hispanic Blacks with no cancer history (OR: 1.09, 95% CI: 0.85 – 1.40), and those with Other race/ethnicity with any cancer history had significant 61% lower odds of specialty care vs. no specialty care compared to those with Other race/ethnicity and no history of cancer (OR: 0.39, 95% CI: 0.21 – 0.71) [Figure 2]. Interaction by NDI was present only after dementia diagnosis when comparing specialty care vs. primary care (p-value: 0.0419); however, when stratified, no overt differences were observed (data not shown).

Evaluating factors associated with specialty care based on cancer type

A sensitivity analysis was conducted to assess if the type of cancer predicted specialty care use. After adjustment for age at dementia diagnosis, sex, race, depression, total anticholinergic burden, NDI, dementia medication use, vascular propensity score, and insurance status, those with prior breast cancer had 31% higher odds of being seen in specialty care vs. no specialty care on dementia diagnosis compared to those with no cancer history (OR: 1.31, 95% CI: 0.92 – 1.87), but this difference was not significant. Similarly, history of colorectal cancer history showed a non-significant 11% increased odds of specialty care use vs. no specialty care use on dementia diagnosis (OR: 1.11, 95% CI: 0.66 – 1.87) compared to those without cancer. Patients with lung cancer had a significant 50% lower odds of specialty care use vs. no specialty care use on dementia diagnosis (OR: 0.50, 95% CI: 0.27 – 0.95) compared to patients without a history of cancer. Although patients with a history of testicular or cervical (OR: 0.44, 95% CI: 0.15 – 1.32) and other cancers (OR: 0.89, 95% CI: 0.75 – 1.06) had lower odds of specialty care vs. no specialty care use on dementia diagnosis, the results were not significant [Table 4]. There was no difference in specialty care use on dementia diagnosis indicated

in those with history of prostate cancer (OR: 1.06, 95% CI: 0.73 – 1.55) or those with two or more cancers (OR: 0.99, 95% CI: 0.74, 1.33) [Table 4].

After dementia diagnosis, results were similar. However, breast cancer now resulted in significant 57% increased odds of specialty care vs. no specialty care (OR: 1.57, 95% CI: 1.04 – 2.37). The associations for colorectal cancer, prostate cancer, testicular or cervical cancers, and two or more cancers changed slightly, but were still not significant (Colorectal: 0.97 [0.54 – 1.75], Prostate: 0.99 [0.66 – 1.49], Testicular / Cervical: 0.58 [0.21 – 1.61], Two or More: 1.12 [0.81 – 1.56]). The associations for lung cancer and other cancers were larger in magnitude and were significant (Lung: 0.31 [0.16 – 0.60], Other: 0.74 [0.62 – 0.89]) [Table 4].

For specialty care use vs. primary care use on dementia diagnosis, no cancer types significantly predicted specialty care use compared to no history of cancer (Breast: 0.98 [0.58 – 1.68], Prostate: 0.66 [0.39 – 1.09], Colorectal: 1.07 [0.48 – 2.36], Lung: 1.77 [0.39 – 8.04], Other: 0.84 [0.64 – 1.11], Testicular / Cervical: 0.51 [0.12 – 2.09], Two or More: 0.93 [0.57 – 1.51]). These results held for specialty care use vs. primary care use after dementia diagnosis. However, other cancers showed significantly decreased odds of specialty care use compared to no cancer history (Other: 0.75 [0.58 – 0.97]) [Table 4].

DISCUSSION

In this evaluation of specialty care use among dementia patients with and without a history of cancer from a university-based health-system in the Southeast, the proportion of specialty care visits on or any time after a dementia diagnosis was lower for those with a history of cancer. Specifically, dementia patients with cancer history demonstrated a 6-

14% lower proportion of specialty care use compared to patients with dementia and no cancer history. Higher age at dementia diagnosis, total anticholinergic burden, NDI, and higher vascular propensity score were all independently predictive of lower odds of a specialty visit on or after dementia diagnosis. Being Non-Hispanic Black was associated with lower odds of specialty visit only on dementia diagnosis. Having had any cancer was independently predictive of specialty visit only after dementia diagnosis, and depression was independently predictive of higher odds of specialty care only after dementia diagnosis. Taking a dementia medication was independently associated with higher odds of a specialty visit both on and after dementia diagnosis. Race/ethnicity modified the association between cancer and use of specialty visits, with those patients from other racial and ethnic backgrounds having 61% lower odds of specialty care use whereas non-Hispanic Blacks and non-Hispanic Whites showed no difference. Lung cancer and cancers other than breast, prostate, colorectal, testicular / cervical, non-melanoma skin, and lung seem to be independently predictive of lower odds of specialty care visit. However, sample sizes for such stratified analyses were small, thus limiting power.

Understanding the reasons behind these associations is important for clinical practice. As mentioned above, the American Cancer Society has released survivorship care guidelines for many common cancers: breast, prostate, colorectal, and head and neck cancer.[19-22] Each of these guidelines recommend primary care physicians monitor cancer survivors for late and long-term effects of cancer and its treatments. The breast cancer guidelines are even more specific about cognition in particular and recommend evaluation and treatment for reversible causes of cognitive impairment with referral to

specialty care where indicated. The results of the current study indicate that despite these guidelines, cancer survivors are significantly less likely to be seen in specialty clinics for evaluation, treatment, and management of dementia. These are important findings given the high prevalence of CRCI after cancer as those with CRCI experience cognitive deficits similar to dementia and may require closer monitoring.

It has been shown that dementia diagnosis is frequently missed or delayed in primary care.[23] Primary care physicians may be less likely to detect new changes in cognition in a patient already experiencing CRCI or may dismiss new changes as related to CRCI concomitant with the aging process, potentially delaying appropriate treatment. Alternatively, primary care physicians may simply be less likely to refer former cancer patients to management in specialty care. In fact, a 2004 survey of 608 family physicians, 624 general internists, and 492 neurologists throughout nine states regarding their willingness to involve specialists, indicated that neurologists prefer specialist involvement in the care of patients needing neurological care across several clinical scenarios more than do primary care physicians.[39] Furthermore, a Canadian study of approximately 700 participants, with about 55% female respondents examining the likelihood of primary and specialty care co-management of patients with chronic diseases, indicated that lower education, lower perceived income, and older age resulted in lower probability of being co-managed by both primary care and specialty care.[40] Studies in more racially diverse populations in the US may suggest these socioeconomic inequities lead to more pervasive disparities in primary and specialty care co-management, especially considering the results of the current study.

Examination of the factors associated with specialty care visits in this population with dementia aids in elucidating areas of improvement clinically. We found that higher age at dementia diagnosis resulted in lower odds of specialty visit. Although this bolsters the hypothesis that cognitive changes may initially be considered as normal aging, in cancer survivors, any cognitive decline in patients, irrespective of age, should be evaluated by a specialist. This is further consistent with primary care physicians being more comfortable diagnosing typical AD presentations, but wanting specialty care confirmation for atypical AD presentations such as those at younger ages.[41] Non-Hispanic Black patients had lower odds of a specialty visit on dementia diagnosis compared to non-Hispanic White patients. It is well known that Blacks are disproportionately affected by both cancer[3,42] and dementia,[43] and frequently have poorer access to appropriate care compared to Whites.[44-46] A previous analysis at UAB, the data source of this study, indicated that although Black patients are not underrepresented across the health system, they do have a lower referral rate to specialty care for Alzheimer's disease.[47] Additionally, many social or cultural differences may affect patient preference and African American representation in specialty care clinics.[48-50] Upon stratification of the association between cancer history and specialty care, it seems that modification of cancer's adverse effect on specialty care use may be driven by the "Other" racial/ethnic category, which is much smaller than Non-Hispanic White and Non-Hispanic Black categories. Further exploration is needed to further confirm these results. We also found that a higher NDI resulted in lower odds of specialty care visit. NDI is a measure of neighborhood disadvantage. Other studies have concluded that neighborhood disadvantage and rural residence lead to poor access to care and health

outcomes.[30,46] There is a shortage of primary care physicians especially in rural areas, which results in further access to care issues in both primary care and access to specialty services.[51] Again, this is an area of clinical / system-wide improvement. Telemedicine or more innovative Extension for Community Healthcare Outcomes (ECHO) approaches can be utilized to reduce racial and socioeconomic disparities in cognitive decline related to lack of specialty care access.[52,53] A systematic review of ECHO programs for many diseases revealed that it is an effective model for improving access to care and health education in rural areas.[54] Four of the reviewed studies were related to dementia care,[55-58] and one of the studies highlighted that ECHO models are effective for improving education and training for primary care physicians in New Mexico.[57] These approaches could be applied to cancer and dementia in Alabama and throughout the Southeast. Collaborative care models could also prove effective. In these models, the primary care physician manages the patient, but consults with specialists for assistance. Dementia-related collaborative care models have shown to be effective to improve function, cognitive ability, and quality of life.[59] Finally, higher total anticholinergic burden and higher vascular propensity score were indicative of lower odds of specialty care visit. This again strengthens the hypothesis that cognitive impairment may be considered a side effect of medications or other conditions, thus having periodic medication reviews, particularly in persons with cognitive issues may be warranted to trigger referral to specialists.

In addition, we found that having depression resulted in higher odds of being seen in specialty care after dementia diagnosis and taking a memory medication resulted in higher odds of being seen in specialty care both on or any time after dementia diagnosis.

Depression is common in older adults,[60] cancer survivors,[61] and dementia patients.[62] Depression also adversely affects cognition.[63] Therefore, the presence of depression may prompt other care providers to encourage follow up with a psychiatrist, neurologist, or geriatrician, who have more experience with cognitive decline and dementia. Additionally, medications for memory are more likely to be prescribed in dementia patients who are seen by specialists, thus continued presence at such clinic.[64]

Finally, these results indicate that certain types of cancer may result in heterogeneity in receipt of specialty care for dementia. In particular, lung cancer demonstrated significantly lower odds of specialty care use. The reasons for this association are unknown, but could potentially be due to a relatively low survival rate for lung cancer or for fear of recurrence rendering the attitude that specialty neurology care may be unnecessary. Cancers other than breast, prostate, colorectal, testicular / cervical, and lung, demonstrated similar results and may be due to similar patterns as hypothesized for lung cancer. Future studies should examine time since cancer diagnosis related to specialty care use for dementia diagnosis and should be designed to evaluate more specific cancer types.

This study has several strengths. First, to our knowledge, this is the first study assessing proportion of specialty care visits among cancer patients with dementia, as well as the first study assessing predictors of this association. Secondly, this study was conducted using real-world clinical data at a large, tertiary medical center in a metropolitan area in the Deep South where both cancer[65] and dementia are highly prevalent.[66] Thirdly, the study population is diverse, with approximately 30% non-Hispanic Black representation. Despite its strengths, this study is not without limitations.

First, some cancer diagnoses may have been missed if diagnosed outside of UAB and not reported to UAB physicians. However, this would bias results toward the null. Secondly, actual referral to specialty care and referrals outside the UAB system were unable to be assessed. Future studies should examine these differences in physician referrals to specialty care rather than simply having a visit in specialty care. Limitations in the EHR and health informatics data should be addressed to ensure accurate collection of referral data. Finally, misclassification in exposures could be present as some medications or diagnoses may have been missed. However, several variables used a multi-pronged approach for identification. Any misclassification would bias results towards the null.

CONCLUSION

Cancer survivors with dementia, particularly those with lung cancer and cancers other than breast, prostate, colorectal, testicular / cervical, and lung are less likely to be seen in specialty care clinics on or after their dementia diagnosis. Several other demographic and health-related factors are associated with specialty care clinic use on or after dementia diagnosis. As specialty visits are typically driven by referral from primary care, understanding primary care physicians' attitudes and level of comfort with diagnosing, treating, and referring cancer survivors for cognitive follow-up; and their attitudes and level of comfort with diagnosing, treating, and referring for dementia is warranted. Educational and professional training programs can be created with goals to provide these health care providers with the appropriate skills to care for cancer survivors, and reduce racial and geographic disparities related to cancer survivorship care and dementia care.

Table 1. Participant Characteristics by Cancer Status.[*]

	History of Cancer (n=2534)	No History of Cancer (n=14544)	p-value
Demographics			
Age at Dementia Diagnosis	77.0 ± 10.0	75.4 ± 11.2	**<0.0001**
Sex			**<0.0001**
Male	1158 (45.7)	6000 (41.3)	
Female	1376 (54.3)	8544 (58.7)	
Race			**<0.0001**
Non-Hispanic White	1682 (66.5)	9052 (62.9)	
Non-Hispanic Black	669 (26.5)	3712 (25.8)	
Other	178 (7.0)	1621 (11.3)	
Marital Status			**0.0007**
Married	1180 (47.7)	5912 (44.1)	
Divorced	234 (9.5)	1282 (9.6)	
Single	316 (12.8)	2119 (15.8)	
Widowed	721 (29.1)	3948 (29.4)	
Other	24 (1.0)	153 (1.1)	
NDI[†]	0.94 ± 0.58	0.96 ± 0.57	0.1212
Insurance Status			**<0.0001**
Private	113 (6.3)	1058 (10.1)	
Government	1673 (92.5)	9163 (87.4)	
Other	22 (1.2)	260 (2.5)	
Health Variables			
Smoking			**<0.0001**
Ever	1239 (51.1)	5637 (43.9)	
Never	1184 (48.9)	7197 (56.1)	
BMI (kg/m^2)[†]	26.4 ± 6.2	26.6 ± 6.3	0.3178
SBP (mmHg)[†]	133.5 ± 23.5	134.8 ± 23.2	**0.0121**
DBP (mmHg)[†]	71.6 ± 11.6	73.1 ± 11.6	**<0.0001**
Glucose Level (mg/dL)[†]	119.9 ± 49.1	119.3 ± 47.5	0.5707
Depression[†]			**<0.0001**
Yes	1452 (66.3)	6346 (57.6)	
No	738 (33.7)	4671 (42.4)	
Dementia Medication[†]			**0.0003**
Yes	822 (32.4)	5264 (36.2)	
No	1712 (67.6)	9280 (63.8)	
Hypertension[†]			**<0.0001**
Yes	1704 (67.6)	8128 (58.4)	
No	815 (32.4)	5779 (41.6)	
Diabetes[†]			**<0.0001**
Yes	482 (19.1)	1891 (13.6)	
No	2037 (80.9)	12016 (86.4)	
Total Anticholinergic Burden[†]	7.7 ± 6.4	5.2 ± 5.2	**<0.0001**

Vascular Propensity Score[†]	0.17 ± 0.04	0.16 ± 0.04	**<0.0001**

[*]Evaluated using t-tests and chi-square tests / Fisher's exact tests (where necessary) for continuous and categorical variables, respectively. Significance set at $\alpha=0.05$
[†]Cancer +: any cancer not including non-melanoma skin cancer or central nervous system cancers; NDI: neighborhood deprivation index based on algorithm published by Ross et al.; BMI: body mass index calculated using height / weight closest to dementia diagnosis within 1 year of diagnosis; SBP: systolic blood pressure, on or closest to dementia diagnosis within 1 year of diagnosis; DBP: diastolic blood pressure, on or closest to dementia diagnosis within 1 year of diagnosis; glucose level: on or closest to dementia diagnosis within 1 year of diagnosis; depression: based on algorithm published by Trinh et al.; dementia medication: donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), memantine (Namenda), and/or donepezil + memantine (Namzaric); hypertension: based on SBP ≥ 140 mmHg / DBP ≥ 90 mmHg, diagnosis of hypertension prior to dementia diagnosis, and/or presence of hypertensive medications prior to dementia diagnosis; diabetes: based on glucose of ≥ 200 mg/dL, diagnosis of diabetes prior to dementia diagnosis, and/or presence of diabetic medications prior to dementia diagnosis; total anticholinergic burden: prior to dementia diagnosis based on algorithm published by Boutstani et al.; vascular propensity score: propensity of chemotherapy exposure based on smoking status, BMI, hypertension status, and diabetes status

Table 2. Proportion of Specialty Visits On or After Dementia Diagnosis by Cancer History Status*

	Yes	No	p-value
Specialty Visit on Dementia Diagnosis			
Cancer History	710 (11.3)	1594 (17.1)	**<0.0001**
No Cancer History	5564 (88.7)	7710 (82.9)	
Specialty Visit After Dementia Diagnosis			
Cancer History	1004 (13.5)	878 (19.2)	**<0.0001**
No Cancer History	6438 (86.5)	3704 (80.8)	
Specialty visit vs. Primary Care on Dementia Diagnosis			
Cancer History	710 (11.3)	262 (18.5)	**<0.0001**
No Cancer History	5564 (88.7)	1154 (81.5)	
Specialty visit vs. Primary Care After Dementia Diagnosis			
Cancer History	1004 (13.5)	312 (21.8)	**<0.0001**
No Cancer History	6438 (86.5)	1120 (78.2)	

*Evaluated using chi-square tests. Significance set as α=0.05. Specialty visit defined as visit in neurology, neurosurgery, psychiatry, or geriatrics. Primary care visit defined as visit in internal medicine or family practice.

Table 3. Factors Associated with Specialty Visits On or After Dementia Diagnosis*

	Specialty Visit vs. No Specialty Visit	
	On Dementia Diagnosis	**After Dementia Diagnosis**
	OR (95% CI)	**OR (95% CI)**
All Cancer vs. No Cancer†	0.94 (0.83-1.07)	**0.85 (0.74-0.98)**
Age at Dementia Diagnosis	**0.97 (0.97-0.98)**	**0.99 (0.98-0.99)**
Male vs. Female	0.94 (0.86-1.04)	0.91 (0.81-1.01)
Black vs. White	**0.61 (0.53-0.70)**	0.95 (0.82-1.10)
Other Race vs. White	1.09 (0.92-1.29)	0.95 (0.77-1.18)
Depression vs. No Depression	1.03 (0.93-1.14)	**1.21 (1.07-1.37)**
Total Anticholinergic Burden	**0.95 (0.94-0.96)**	**0.97 (0.96-0.99)**
NDI†	**0.89 (0.80-0.98)**	**0.80 (0.71-0.89)**
Dementia Meds vs. No Dementia Meds†	**1.92 (1.74-2.12)**	**3.15 (2.81-3.53)**
Vascular Propensity Score	**0.01 (0.00-0.03)**	**0.20 (0.05-0.79)**
Private vs. Other Insurance	**2.44 (1.64-3.63)**	**1.57 (1.02-2.41)**
Government vs. Other Insurance	1.44 (0.99-2.09)	1.38 (0.92-2.07)
	Specialty Visit vs. Only Primary Care Visit	
	On Dementia Diagnosis	**After Dementia Diagnosis**
	OR (95% CI)	**OR (95% CI)**
All Cancer vs. No Cancer	0.85 (0.70-1.05)	**0.80 (0.66-0.98)**
Age at Dementia Diagnosis	**0.97 (0.96-0.97)**	**0.97 (0.97-0.98)**
Male vs. Female	1.02 (0.86-1.20)	0.96 (0.82-1.14)
Black vs. White	**0.43 (0.34-0.53)**	**0.60 (0.48-0.74)**
Other Race vs. White	1.26 (0.92-1.72)	0.85 (0.61-1.19)
Depression vs. No Depression	1.04 (0.87-1.23)	1.14 (0.95-1.36)
Total Anticholinergic Burden	0.99 (0.98-1.01)	**0.97 (0.96-0.99)**
NDI	1.07 (0.91-1.26)	0.95 (0.81-1.12)
Dementia Meds vs. No Dementia Meds†	0.97 (0.83-1.14)	**2.23 (1.88-2.63)**
Vascular Propensity Score	**0.01 (0.001-0.08)**	**0.01 (0.00-0.05)**
Private vs. Other Insurance	1.00 (0.42-2.38)	1.11 (0.56-2.19)
Government vs. Other Insurance	0.71 (0.31-1.63)	1.27 (0.67-2.40)

*Evaluated using logistic regression adjusted for all variables. Significance set at α=0.05. Specialty visit defined as visit in neurology, neurosurgery, psychiatry, or geriatrics. Primary care defined as visit in internal medicine or family practice.
†All cancer: not including non-melanoma skin cancer or central nervous system cancers; NDI: neighborhood deprivation index; memory medication: donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), memantine (Namenda), donepezil + memantine (Namzaric)

Table 4. Association Between Cancer History Type On Specialty Visits On or After Dementia Diagnosis*

	Specialty Visit vs. No Specialty Visit	
	On Dementia Diagnosis	**After Dementia Diagnosis**
	OR (95% CI)	**OR (95% CI)**
No Cancer	1.00 (Ref)	1.00 (Ref)
Breast	1.31 (0.92-1.87)	**1.57 (1.04-2.37)**
Prostate	1.06 (0.73-1.55)	0.99 (0.66-1.49)
Colorectal	1.11 (0.66-1.87)	0.97 (0.54-1.75)
Testicular / Cervical	0.44 (0.15-1.32)	0.58 (0.21-1.61)
Lung	**0.50 (0.27-0.95)**	**0.31 (0.16-0.60)**
Other	0.89 (0.75-1.06)	**0.74 (0.62-0.89)**
Two or More	0.99 (0.74-1.33)	1.12 (0.81-1.56)
	Specialty Visit vs. Only Primary Care Visit	
	On Dementia Diagnosis	**After Dementia Diagnosis**
	OR (95% CI)	**OR (95% CI)**
No Cancer	1.00 (Ref)	1.00 (Ref)
Breast	0.98 (0.58-1.68)	0.92 (0.55-1.54)
Prostate	0.66 (0.39-1.09)	0.74 (0.45-1.24)
Colorectal	1.07 (0.48-2.36)	0.91 (0.40-2.04)
Testicular / Cervical	0.51 (0.12-2.09)	0.60 (0.17-2.17)
Lung	1.77 (0.39-8.04)	0.66 (0.21-2.05)
Other	0.84 (0.64-1.11)	**0.75 (0.58-0.97)**
Two or More	0.93 (0.57-1.51)	1.05 (0.66-1.67)

*Evaluated using logistic regression adjusted for age at dementia diagnosis, sex, race, depression, total anticholinergic burden, NDI, insurance status, dementia medication use, and vascular propensity score. Significance set at α=0.05. Specialty visit defined as visit in neurology, neurosurgery, psychiatry, or geriatrics. Primary care defined as visit in internal medicine or family practice.

†NDI: neighborhood deprivation index; dementia medication: donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), memantine (Namenda), donepezil + memantine (Namzaric)

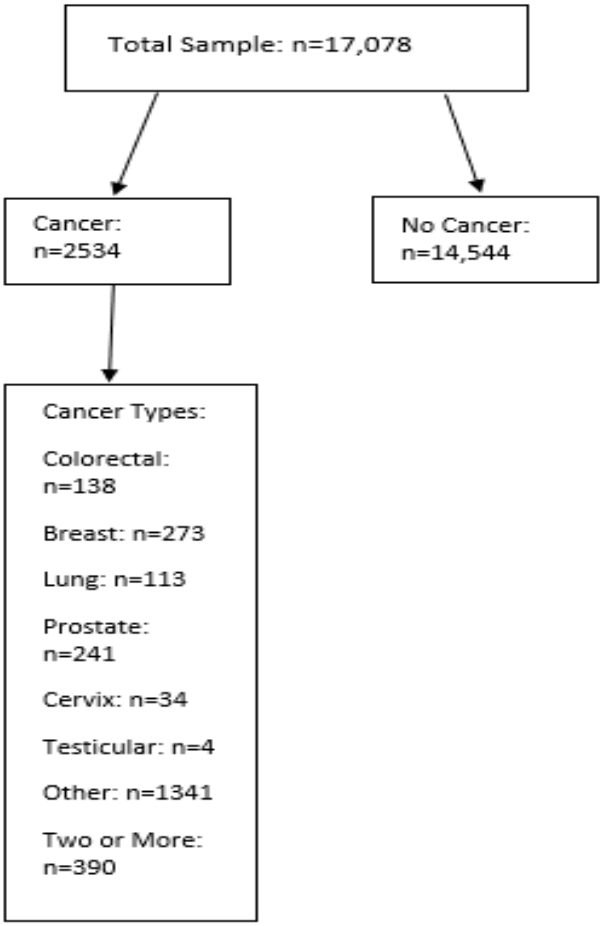

Figure 1. Flow Chart of Participants. Those with history of only non-melanoma skin cancer were not included in the cancer group.

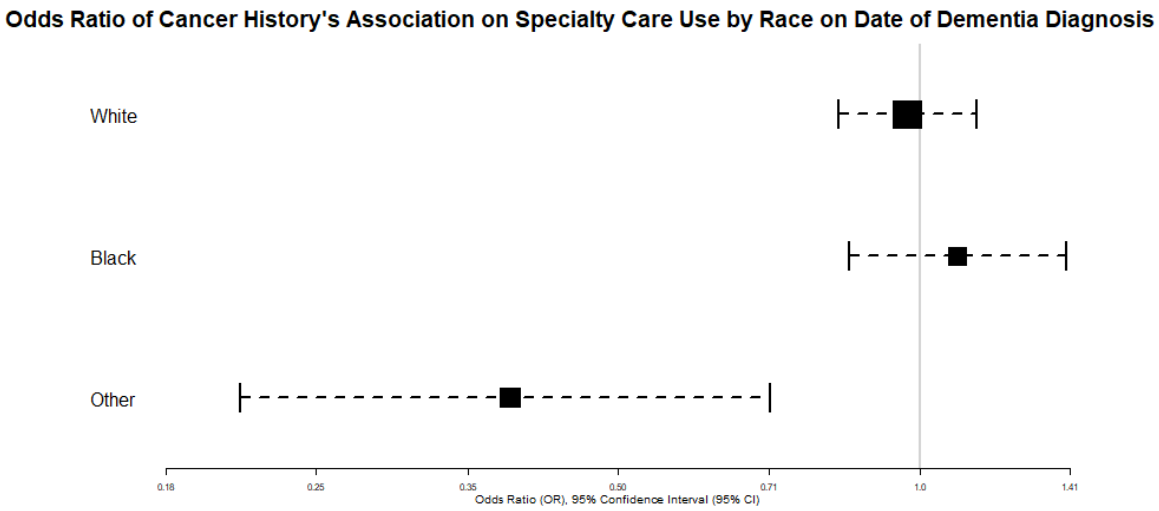

Figure 2. Forest Plot of the Association Between Any Cancer History and Specialty Care Use by Race. No difference in the association between any cancer history and specialty care use on the date of dementia diagnosis was seen between non-Hispanic White and non-Hispanic Black participants with dementia. However, those with other race/ethnicity had significantly lower odds of specialty care use on the date of dementia diagnosis.

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SUPPLEMENTARY MATERIAL

Supplementary Table of Diagnosis Codes / Medications Used for Primary Outcome, Primary Exposure, and Comorbidity Classification			
	ICD-9 Codes	**ICD-10 Codes**	**Medications**
All-Cause Dementia			
Alzheimer's Disease	331.0	G30.9; G30.1; G20.8	
Vascular	290.40; 290.41; 290.42; 290.43; 331.82	F01.50; F01.51	
Dementia with Lewy Bodies	331.82	G31.83	
Frontotemporal	331.1; 331.11; 331.19	G31.0; G31.01; G31.09	
Alcohol Induced	291.2	F10.26; F10.27; F10.97	NA
Other (Creutzfeld-Jakob Disease, Huntington's Disease, Drug-Induced)	046.11; 046.19; 292.82; 333.4	A81.00; A81.01; A81.09; F19.27; F13.27; F13.97; F18.97; F19.17; F19.97; G10	
Not Otherwise Specified	290.0; 290.10; 290.11; 290.12; 290.13; 290.20; 290.21; 290.3; 290.9; 294.1; 294.10; 294.11; 294.20; 294.21; 294.8; 331.2; 787	F03.90; F03.91; F05; F02.80; F02.81; F06.0; F06.8; R41.81; G31.1; R41.9	
Cancer			
Breast	174.0-174.9	C50.011-C50.929; EXCLUDING C50.021-C50.029; C50.121-C50.129; C50.221-C50.229; C50.321-C50.329; C50.421-C50.429; C50.521-C50.529; C50.621-C50.629; C50.821-C50.829; C50.921-C50.929	NA
Colorectal	153.0-153.9; 154.0-154.1	C18.0-C18.9; C19; C20	
Prostate	185	C61	

Lung	162.0-162.9	C33; C34.00-C34.92	
Cervical	180.0-180.9	C53.0-C53.9	
Testicular	186.0-186.9	C62.00-C62.92	
Non-Melanoma Skin	173.00-173.99	C44.00-C44.99	NA
Other	All others from 140.0-208.92	All others from C00.0-C96.Z	
Depression			
	290.13; 290.21; 290.43; 296.2; 296.3; 296.82; 296.9; 296.99; 298; 300.4; 301.1; 305.8; 305.81; 309; 309.1; 311; 969	F32.0; F32.1; F32.2; F32.4; F32.5; F32.9; F33.0; F33.1; F33.2; F33.3; F33.8; F33.9; F34.1; F43.21; F43.23	Amitriptyline; Bupropion; Citalopram; Climipramine; Desipramine; Doxepin; Duloxetine; Escitalopram; Fluoxetine; Fluvoxamine; Imipramine; Maprotiline; Mirtazapine; Nefazodone; Nortriptyline; Paroxetine; Phenelzine; Protriptyline; Sertraline; Selegiline patch; Tranylcypromine; Trimipramine; Venlafaxine ***If on these medications, but with the following codes not considered depressed:** ICD-9: 300.00; 300.01; 300.02; 300.09; 309.81; 338 ICD-10: F41.0; F41.1; F41.3; F41.8; F41.9; F43.10; G89.0-G89.4

Hypertension			
	401.x; 403.0x; 403.1x; 403.9x	I10; I12.0; I12.9; I16.x	Chlorothiazide; Chlorthalidone; Hydrochlorothiazide; Indapamide; Metolazone; HCTZ; Benazepril; Captopril; Enalapril; Fosinopril; Lisinopril; Moexipril; Perindopril; Quinapril; Ramipril; Trandolapril; Azilsartan; Candesartan; Eprosartan; Irbesartan; Losartan; Olmesartan; Telmisartan; Valsartan; Amlodipine; Felodipine; Isradipine; Nicardipine; Nifedipine; Nisoldipine; Diltiazem; Verapamil; Bumetanide; Furosemide; Torsemide; Amiloride; Triamterene; Eplerenone; Spironolactone; Atenolol; Betaxolol; Bisoprolol; Metoprolol; Nebivolol; Nadolol; Propranolol; Acebutolol; Carteolol; Penbutolol; Pindolol; Carvedilol; Labetalol; Aliskiren;

			Doxazosin; Prazosin; Terazosin; Clonidine; Methyldopa; Guanfacine; Hydralazine; Minoxidil
Diabetes			
	250.xx; 357.2; 362.0x; 366.41	E08.36; E08.42; E09.36; E09.42; E10.10; E10.11; E10.29; E10.311; E10.319; E10.36; E10.39; E10.40; E10.42; E10.51; E10.618; E10.620; E10.621; E10.622; E10.628; E10.630; E10.638; E10.641; E10.649; E10.65; E10.69; E10.8; E10.9; E11.00; E11.01; E11.29; E11.311; E11.319; E11.329; E11.339; E11.349; E11.359; E11.36; E11.39; E11.40; E11.42; E11.51; E11.618; E11.620; E11.621; E11.622; E11.628; E11.630; E11.638; E11.641; E11.649; E11.65; E11.69; E11.8; E11.9; E13.10; E13.36; E13.42; E10.37X1; E10.37X2; E10.37X3; E10.37X9; E11.10; E11.11; E11.3291; E11.3292; E11.3293; E11.3299; E11.3391; E11.3392;	Cycloset; Acarbose; Acetohexamide; Albiglutide; Alogliptin; Canagliflozin; Chlorpropamide; Dapagliflozin; Dulaglutide; Empagliflozin; Ertugliflozin; Exenatide; Exenatide ER; Glibenclamide; Glimepiride; Glipizide; Glyburide; Linagliptin; Liraglutide; Lixisenatide; Metformin; Miglitol; Nateglinide; Pioglitazone; Pramlintide; Repaglinide; Rosiglitazone; Saxagliptin; Semaglutide; Sitagliptin; Tolazamide; Tolbutamide; Inhaled insulin; Insulin; Insulin aspart; Insulin degludec; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin human NPH; Insulin

	E11.3393; E11.3399; E11.3491; E11.3492; E11.3493; E11.3499; E11.3591; E11.3592; E11.3593; E11.3599; E11.37X2	human regular; Insulin lispro

DISCUSSION

The current studies of the effects of cancer and its treatments on dementia revealed that those with cancer history begin with cognition approximately 1.5 points higher at dementia baseline, but that this association is confounded by health behaviors, comorbidities, and medications. Additionally, among patients with dementia and history of cancer, those taking immunotherapies demonstrate lower cognition at dementia baseline and progress approximately 3 points slower whereas those on chemotherapies, hormone therapies, or two or more therapies demonstrate faster decline. Finally, those with cancer history were less likely to utilize specialty care for neurological concerns especially non-Hispanic Blacks and the socioeconomically disadvantaged.

Our prior study examined the overall association between cancer history and Alzheimer's disease in the Alzheimer's Disease Neuroimaging Initiative cohort, but had many limitations.[22] The first of the current studies examines a similar effect in a more externally valid population and with reduced possibility of both selection and information bias. Additionally, studies have indicated negative cognitive effects for cancer treatments[14,23-41] and poor access to care,[53] but none have evaluated the effects of these on cognitive progression among dementia patients specifically. The latter two of the current studies do examine the effects of specific cancer treatments and care patterns among dementia patients with and without cancer history.

From these studies, many limitations remained despite its strengths. Future studies should examine this association in a larger study with ability to stratify by cancer type, control for cancer staging, and to examine more detailed cancer treatment information. Confirmation of these results in larger, more robust samples could lead to interventions for care and treatment of both cancer and dementia patients. Additionally, system wide improvements in access to care and primary care follow-up can be developed and implemented. These interventions can eventually lead to decreased cognitive burden among cancer survivors and improved outcomes among both cancer and dementia patients.

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APPENDIX

UAB IRB STUDY APPROVALS

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
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APPROVAL LETTER

TO: Fowler, Mackenzie E

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 03-Oct-2019

RE: IRB-300003929
Progression of Alzheimer's Disease by Prior Breast Cancer Diagnosis

---

The IRB reviewed and approved the Initial Application submitted on 27-Sep-2019 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Exempt
Exempt Categories:	4
Determination:	Exempt
Approval Date:	03-Oct-2019
Approval Period:	No Continuing Review

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA

Documents Included in Review:

- HSP.clean.190927
- waiverauth.190916
- IRB PERSONNEL FORM

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APPROVAL LETTER

TO: Fowler, Mackenzie E

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 29-Oct-2019

RE: IRB-300003929
Progression of Alzheimer's Disease by Prior Breast Cancer Diagnosis

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The IRB reviewed and approved the Revision/Amendment submitted on 11-Oct-2019 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Exempt
Exempt Categories:	4
Determination:	Exempt
Approval Date:	29-Oct-2019

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA

Documents Included in Review:

- praf.191011

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APPROVAL LETTER

TO: Fowler, Mackenzie E

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 30-Mar-2020

RE: IRB-300003929
Progression of Alzheimer's Disease by Prior Breast Cancer Diagnosis

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The IRB reviewed and approved the Revision/Amendment submitted on 25-Mar-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Exempt
Exempt Categories:	4
Determination:	Exempt
Approval Date:	30-Mar-2020

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA

Documents Included in Review:

- praf.200325

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APPROVAL LETTER

TO: Fowler, Mackenzie E

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 04-Jun-2020

RE: IRB-300003929
Progression of Alzheimer's Disease by Prior Breast Cancer Diagnosis

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The IRB reviewed and approved the Revision/Amendment submitted on 01-Jun-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Exempt
Exempt Categories: 4
Determination: Exempt
Approval Date: 04-Jun-2020

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA

Documents Included in Review:

- praf.200601

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APPROVAL LETTER

TO: Fowler, Mackenzie E

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

IORG Registration # IRB00012550 (IRB 03)

DATE: 15-Oct-2020

RE: IRB-300003929-006
Progression of Alzheimer's Disease by Prior Breast Cancer Diagnosis

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The IRB reviewed and approved the Revision/Amendment submitted on 13-Oct-2020 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Exempt
Exempt Categories:	4,
Determination:	Exempt
Approval Date:	15-Oct-2020

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA

Documents Included in Review:

- REVISION/AMENDMENT EFORM

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: The Determination for the submission will be "Approved."
3. In the list of documents, select and download the desired approved documents. The stamped consent/assent form(s) will be listed with a category of Consent/Assent Document

(CF, AF, Info Sheet, Phone Script, etc.)